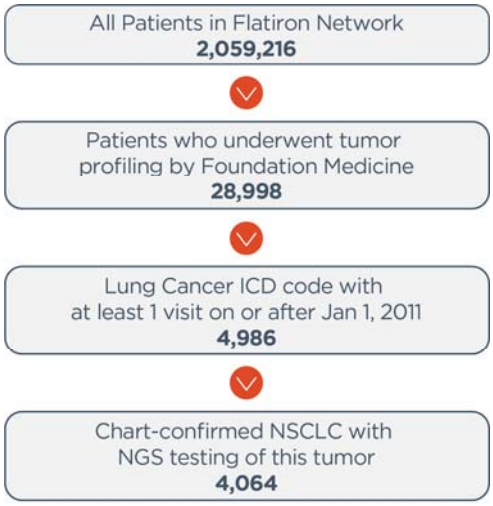
Supplementary Online Content

Singhal G, Miller PG, Agarwala V, et al. Association of patient characteristics and tumor genomics with clinical outcomes among patients with non–small cell lung cancer using a clinicogenomic database. *JAMA*. doi:10.1001/jama.2019.3241

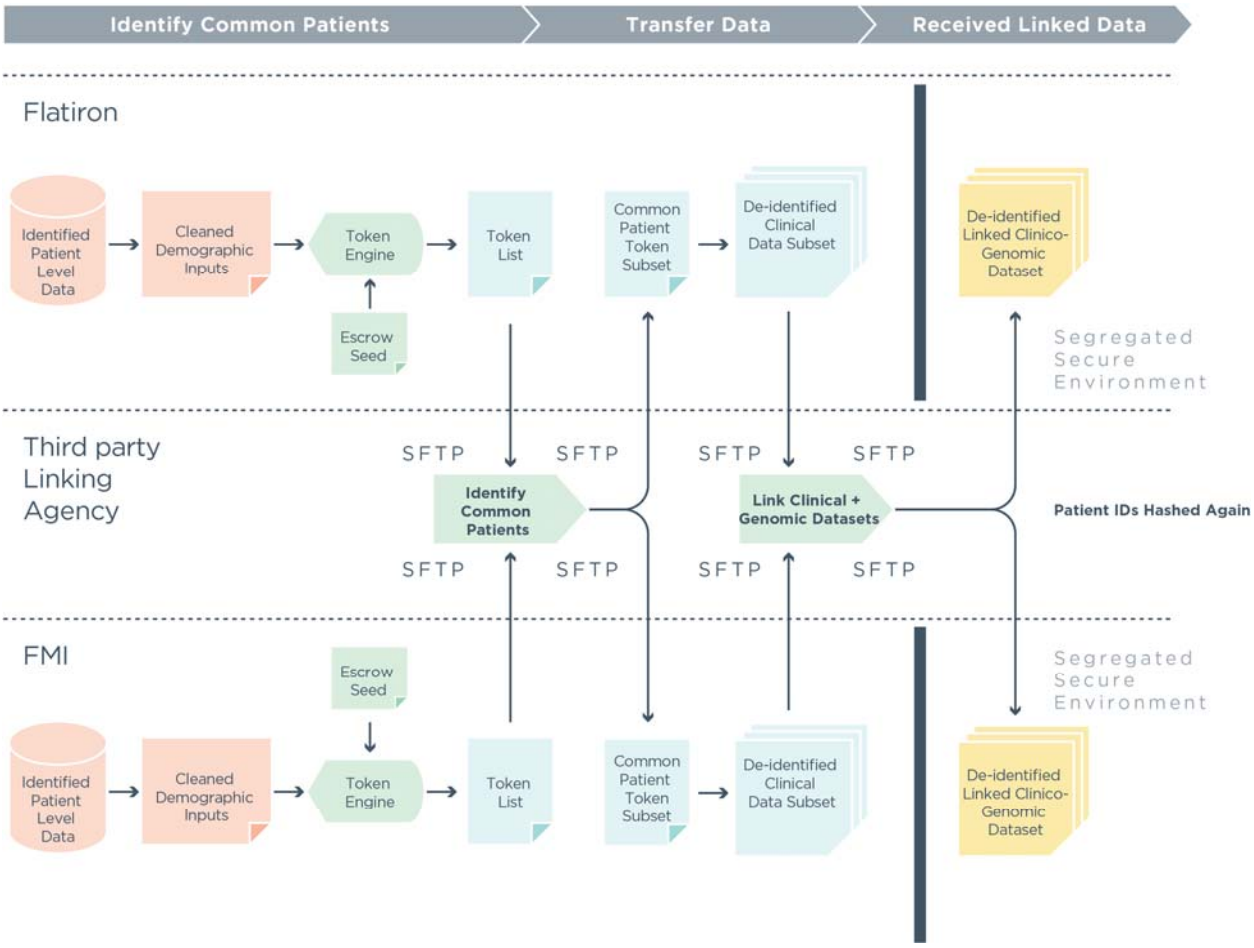
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Generation of the Clinico-Genomic Database (CGDB)

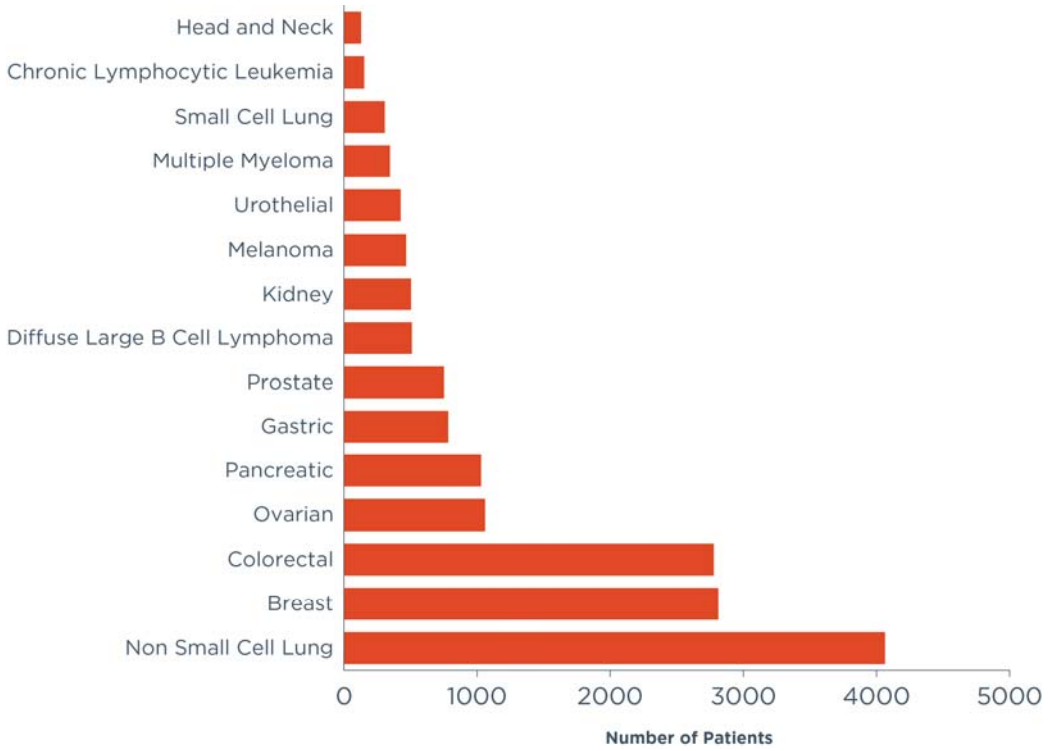
A



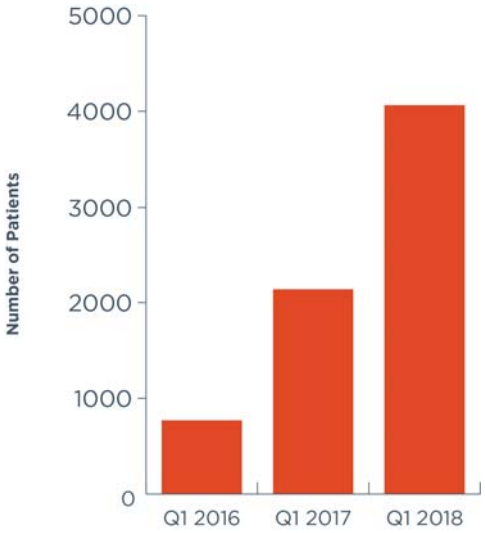
B



C



D

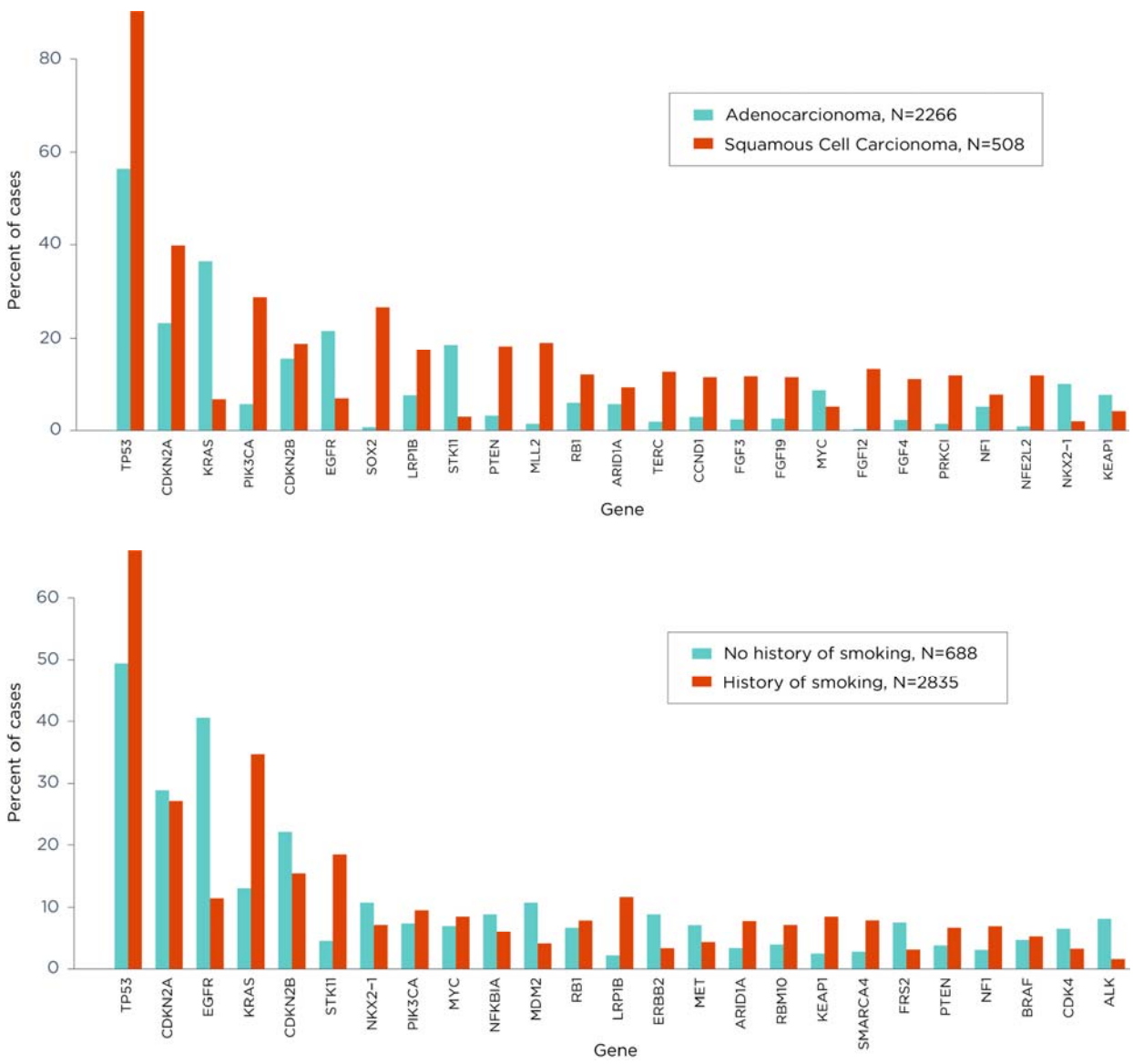


eFigure 1: Generation of the Clinico-Genomic Database (CGDB)

(a) Generation of overall CGDB and Non-Small Cell Lung Cancer (NSCLC) cohort
(b) Health Insurance Portability and Accountability Act (HIPAA)-compliant workflow for linking patient-level clinical and genomic information
(c) Estimated composition of the CGDB by tumor subtype, as of January 1, 2018
(d) Estimated quarterly growth of the NSCLC cohort within the CGDB over time

eFigure 2. Genomic Characteristics of Patients in NSCLC Cohort

A



B

DRIVER	FUSION PARTNER	FREQUENCY
ALK	EML4	90
	STRN	2
	DCTN1	2
	OTHER	23
ROS1	CD74	12
	EZR	5
	TPM3	3
	SDC4	2
	OTHER	10
RET	KIF5B	27
	CDC6	10
	NCOA4	2
	OTHER	6

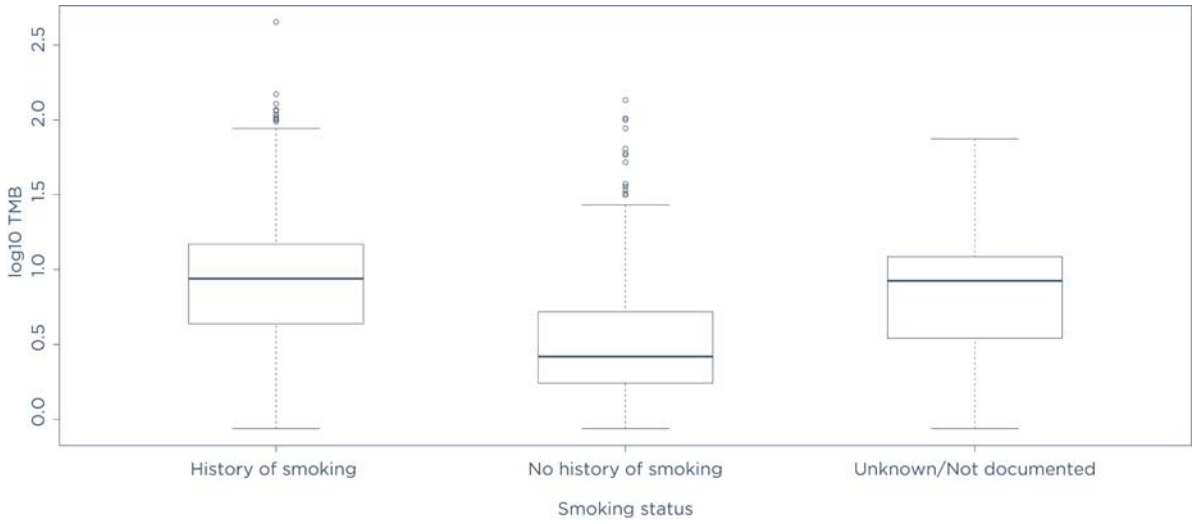
eFigure 2: Genomic Characteristics of Patients in NSCLC Cohort

(a) Distribution of mutations stratified by pathology (top) and smoking status (bottom)*
(b) Translocation partners of *ALK*, *ROS1*, and *RET* in NSCLC cohort

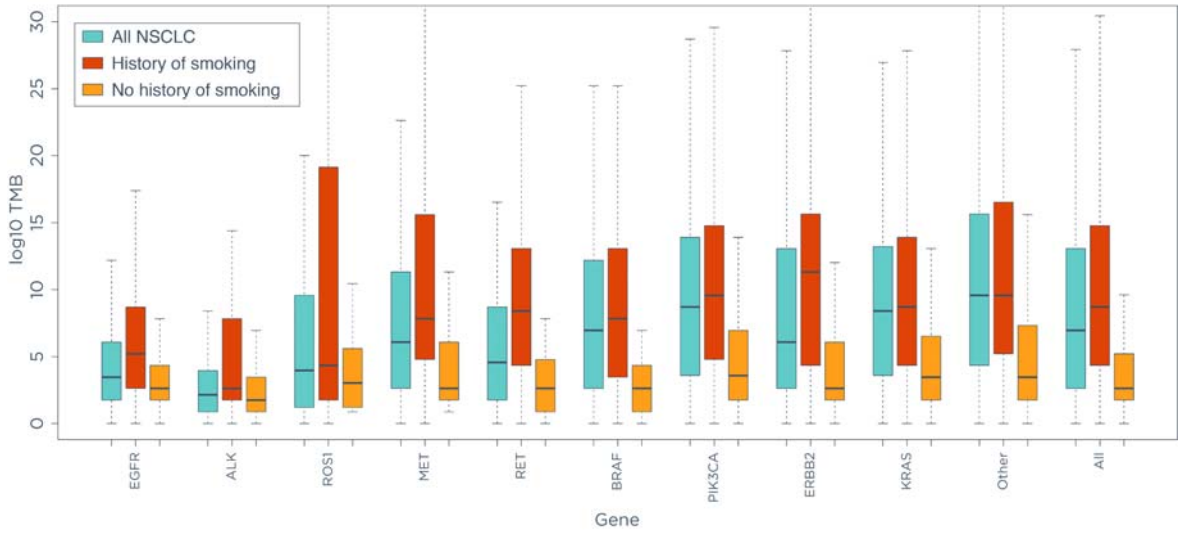
*For purposes of uniformity, only data from patients for whom tumor sequencing was done on the most updated FoundationOne platform (see eTable 1) are presented here.

eFigure 3. Analysis of Tumor Mutation Burden (TMB) in NSCLC Cohort

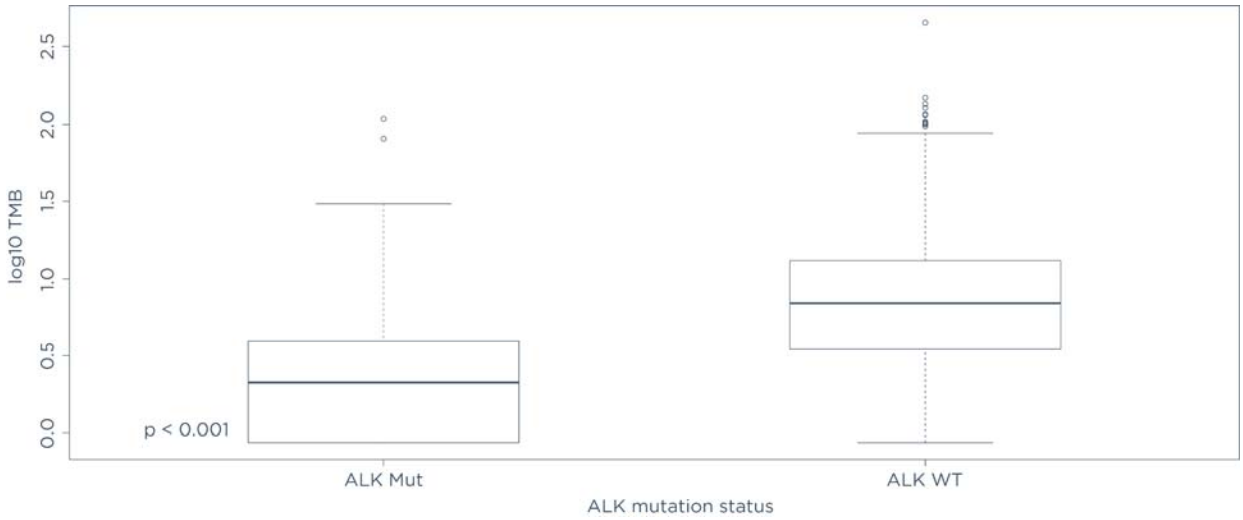
A



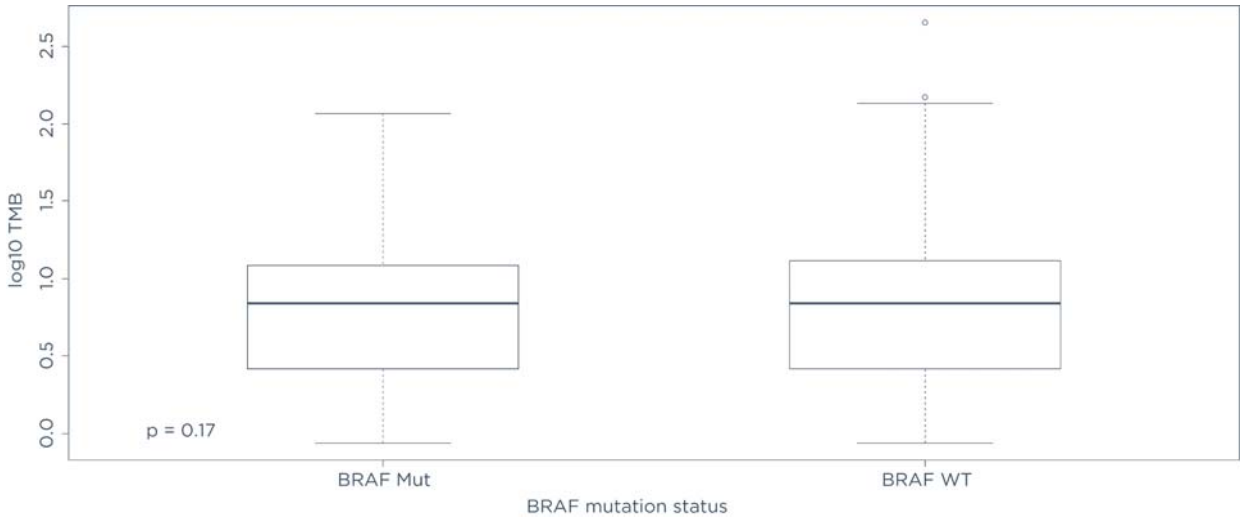
B



C – *ALK*

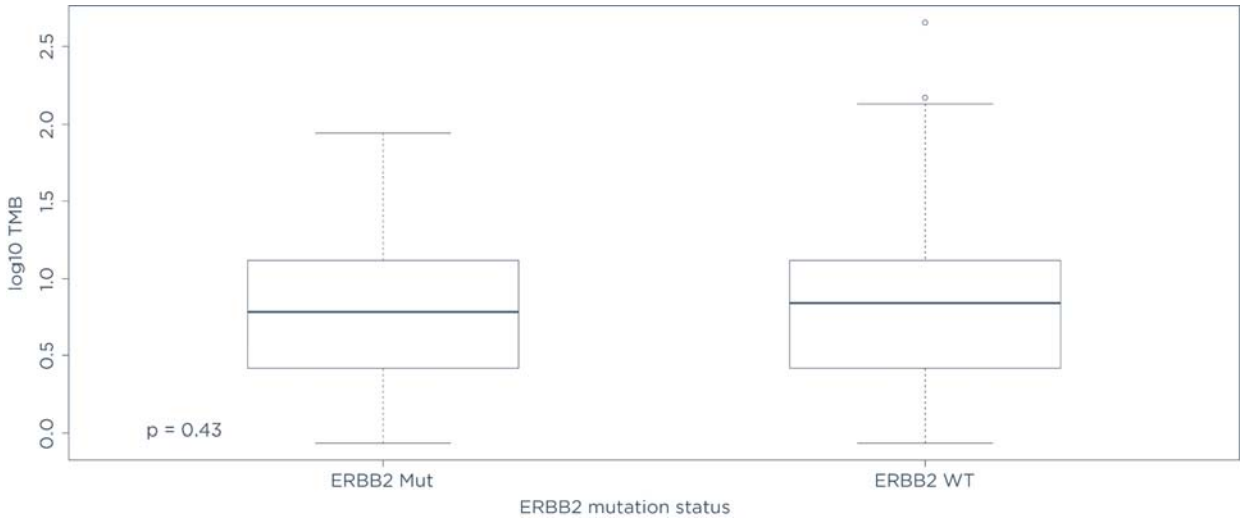


C – *BRAF*

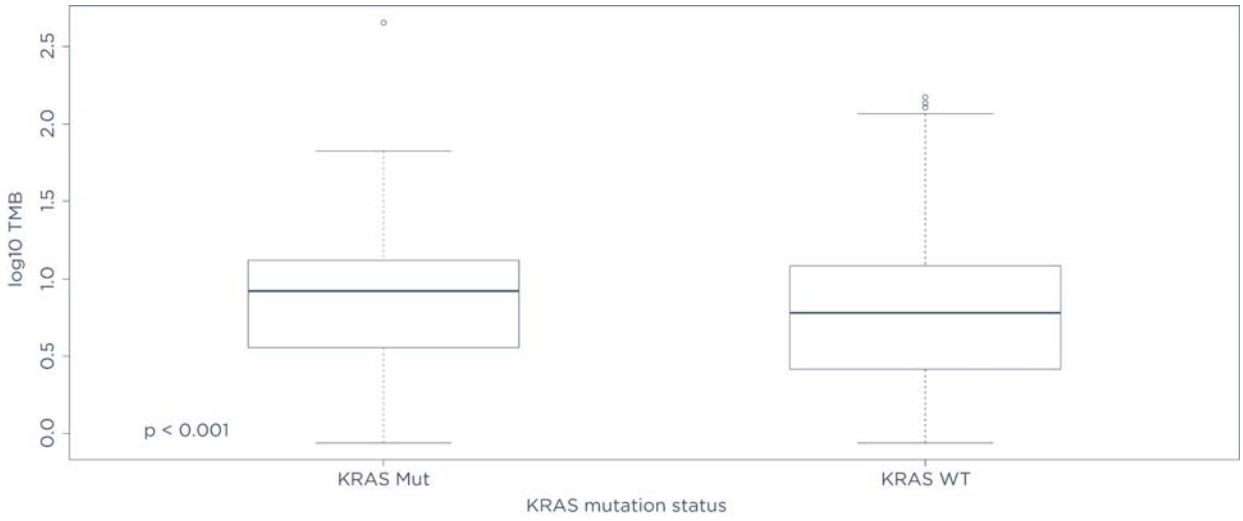


C – *EGFR*

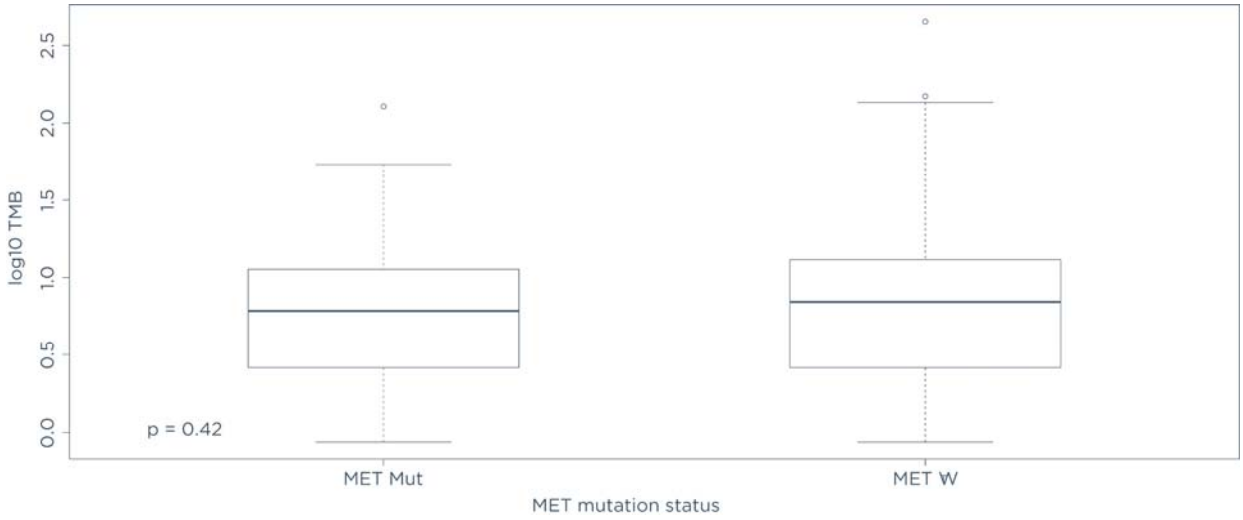
C – *ERBB2*



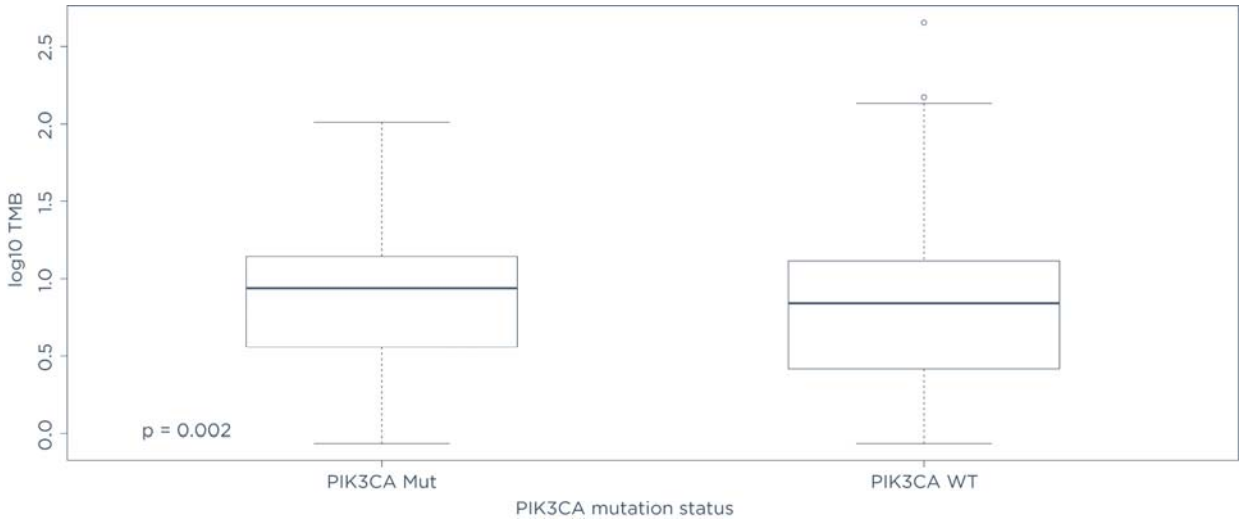
C – *KRAS*



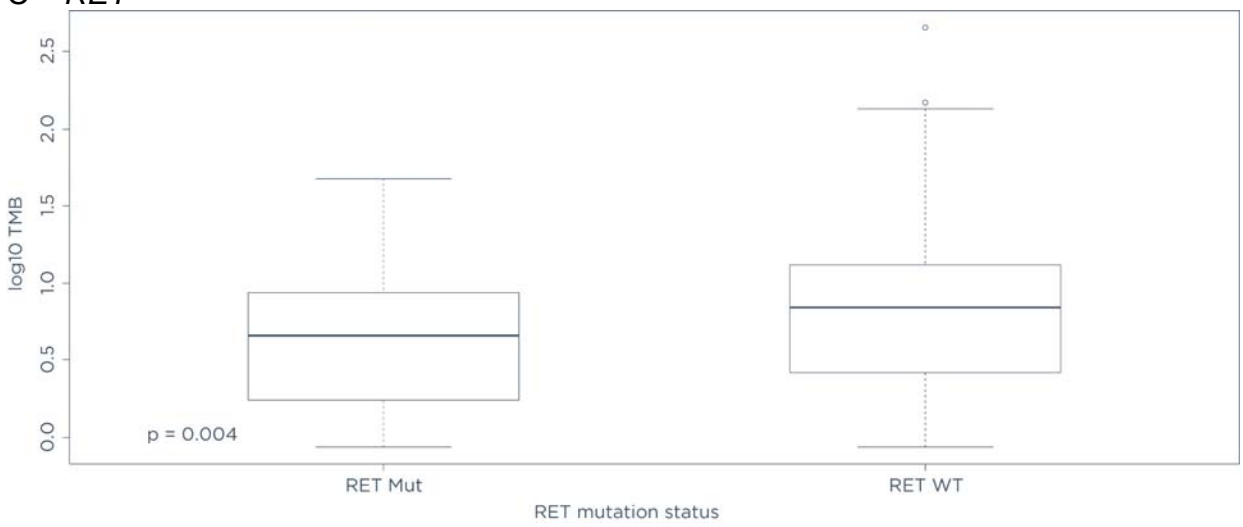
C – *MET*



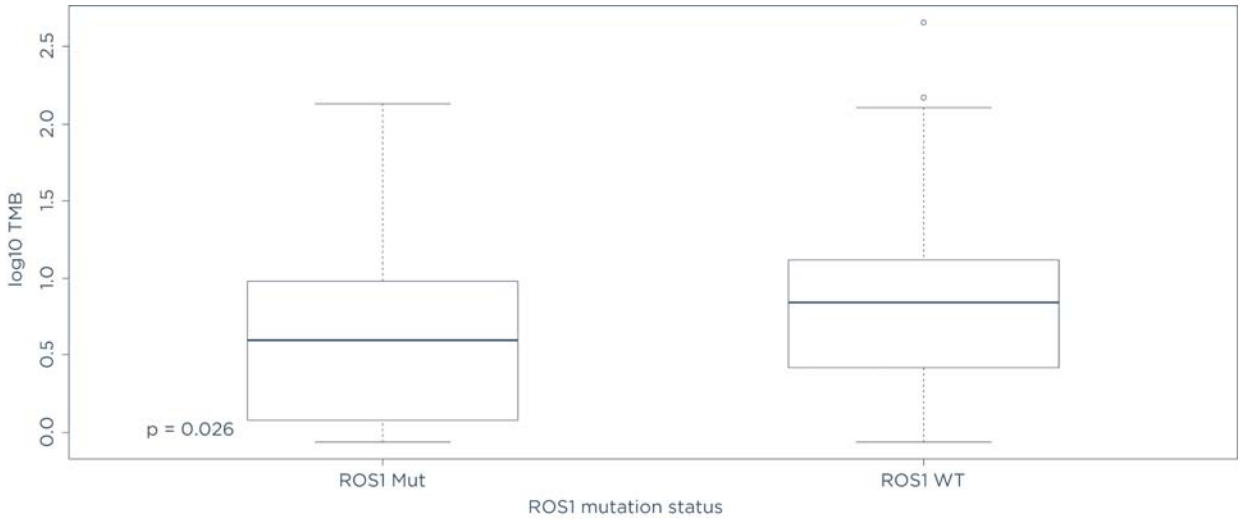
C – *PIK3CA*



C – *RET*



C – *ROS1*



eFigure 3: Analysis of Tumor Mutation Burden (TMB) in NSCLC Cohort

(a) Comparison of median tumor mutational burden between patients with and without a history of smoking*
(b) Distribution of median tumor mutational burden stratified by presence of genetic mutation for all patients (green), those with a history of smoking (red), and those without a history of smoking (orange)
(c) Comparison of median tumor mutational burden between presence or absence of specified genetic mutation*

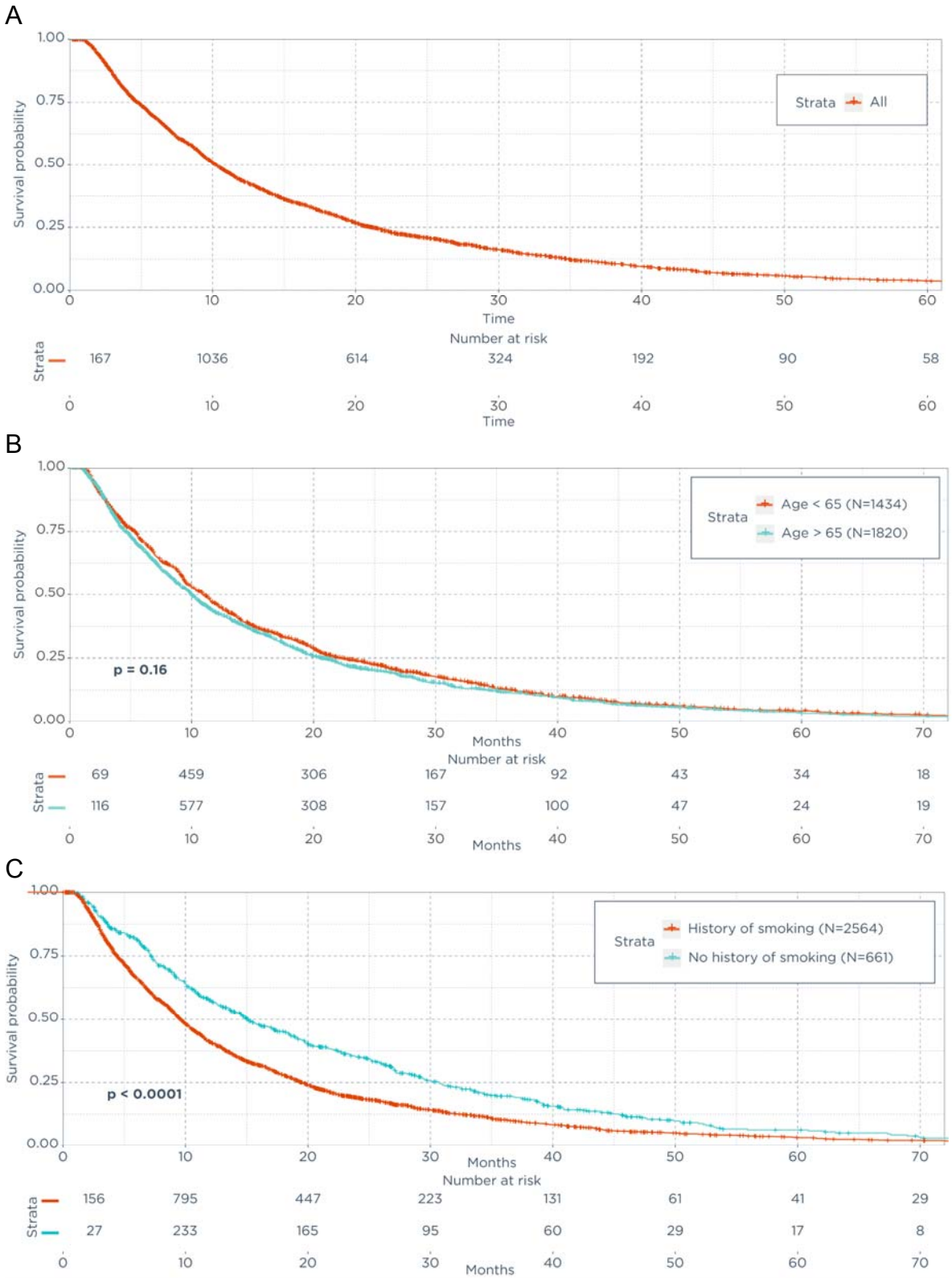
* The heavy horizontal line is the median, the top and bottom edges of the box correspond to the upper and lower 25% respectively, the error bar extends to 1.5 times the interquartile range from the edge of the box, the open circles are outliers.

eFigure 4. Genomic and Clinical Features in NSCLC Dataset

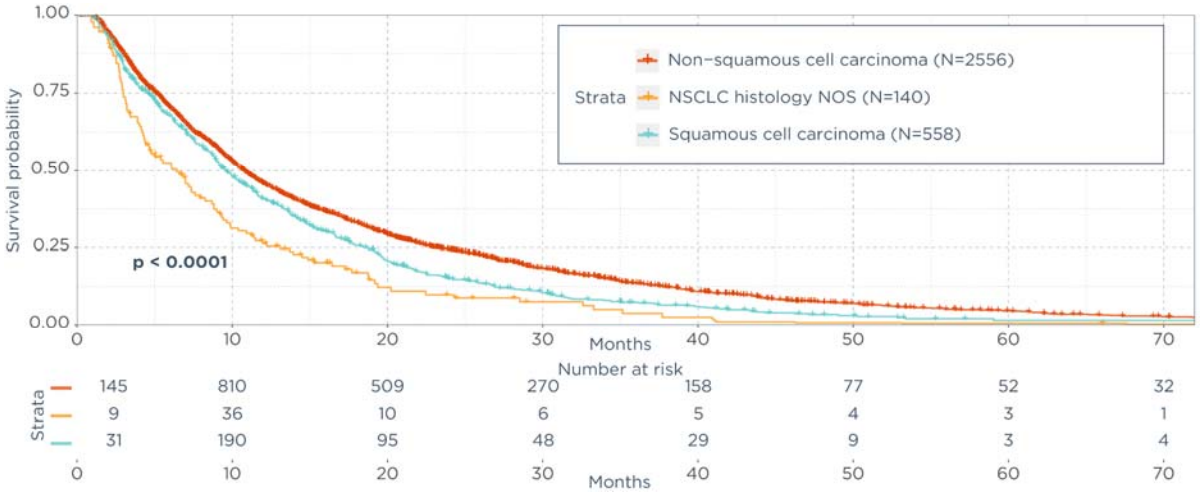
eFigure 4: Genomic and Clinical Features in NSCLC Dataset

Each patient is represented by a column in the heatmaps which define tumor mutational burden, gender, smoking status, pathology, stage of disease, mutational status of most commonly mutated and NCCN-driver genes, and type of mutation identified.

eFigure 5. Clinical Predictors of Overall Survival in NSCLC



D

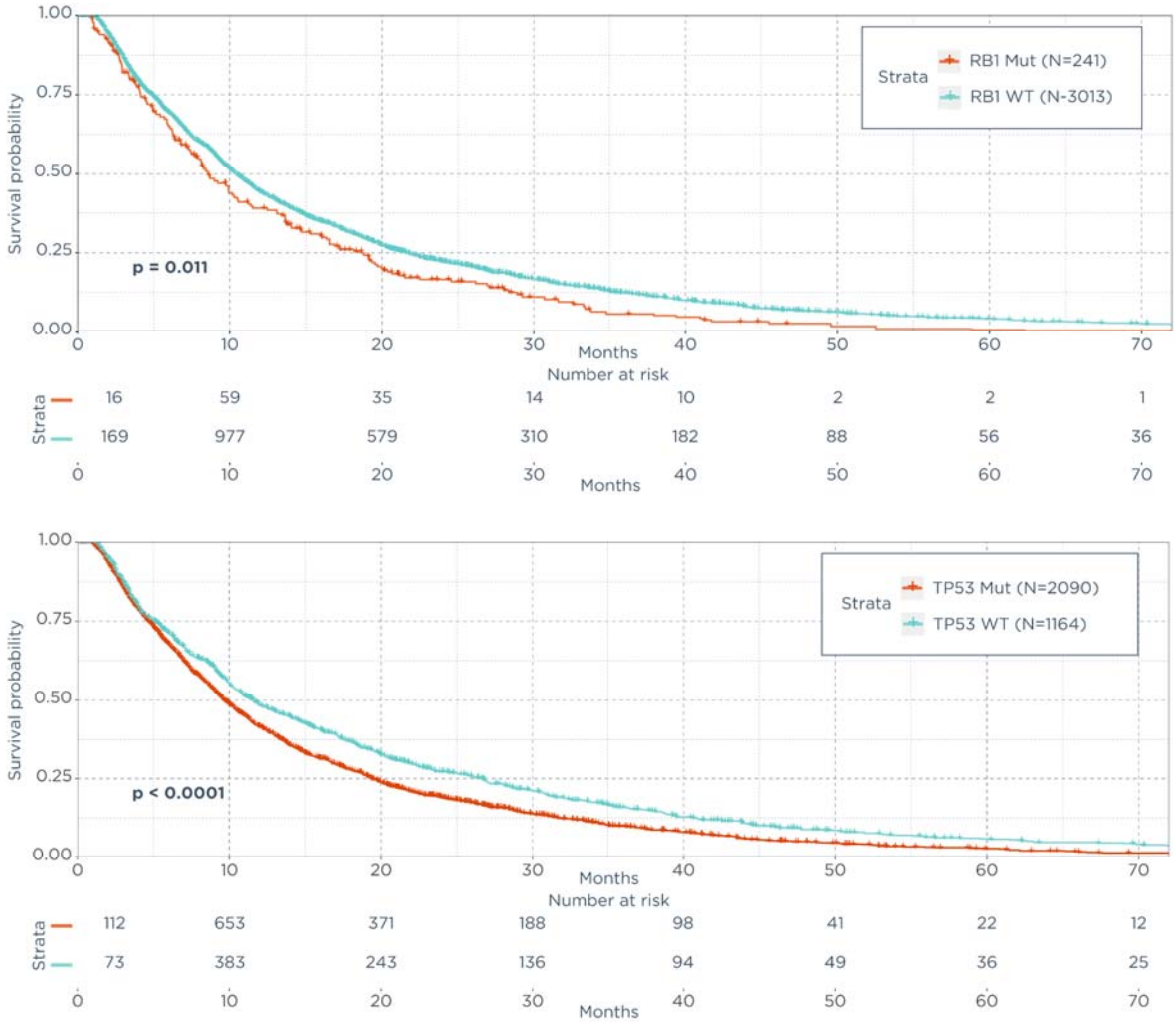


eFigure 5: Clinical Predictors of Overall Survival in NSCLC

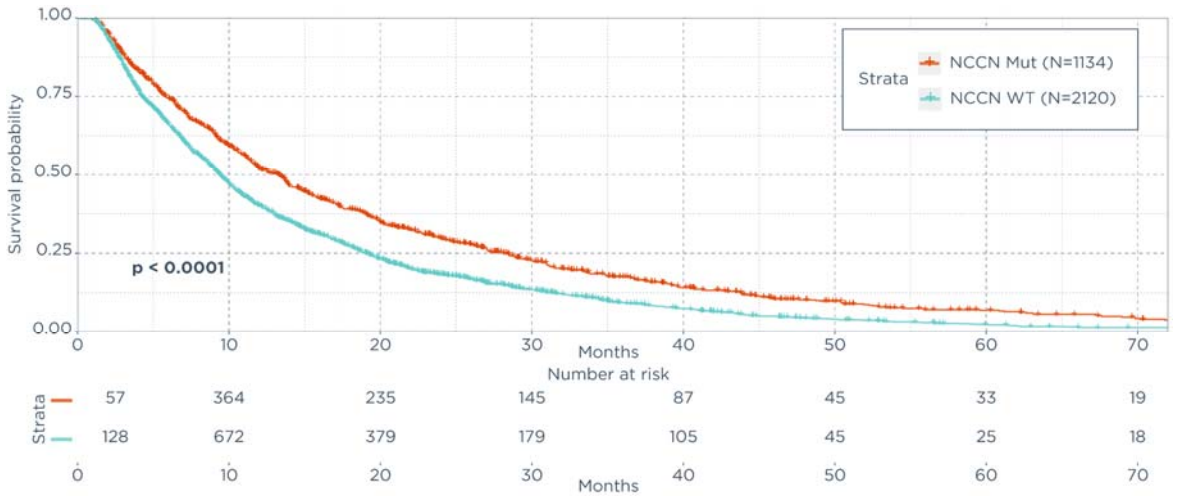
(a) Overall survival of patients from advanced diagnosis
(b) Overall survival of patients from advanced diagnosis stratified by age greater or less than 65 years old at advanced diagnosis
(c) Overall survival of patients from advanced diagnosis stratified by smoking history
(d) Overall survival of patients from advanced diagnosis stratified by pathology

eFigure 6. Genomic Predictors of Survival and Therapy Response

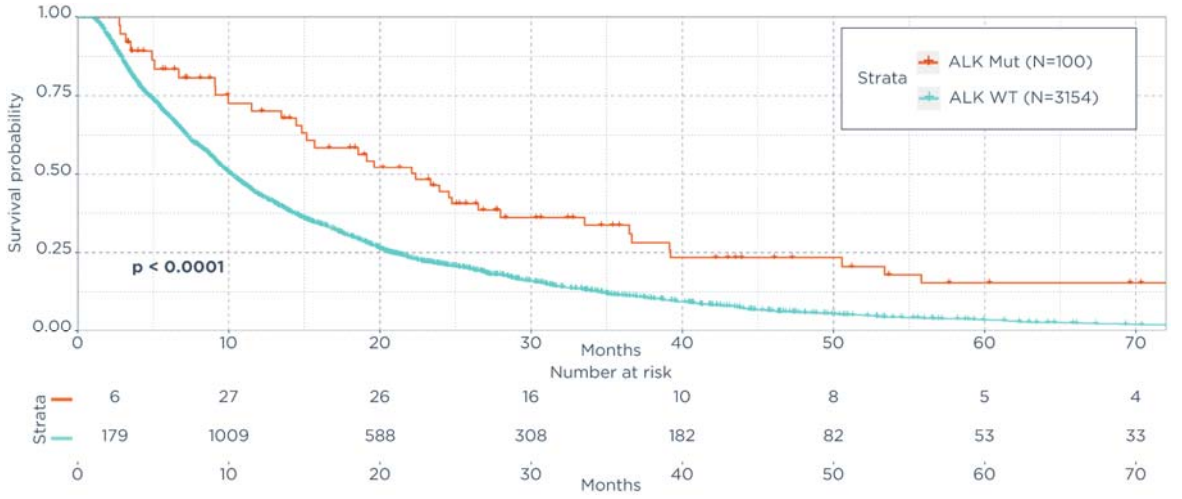
A



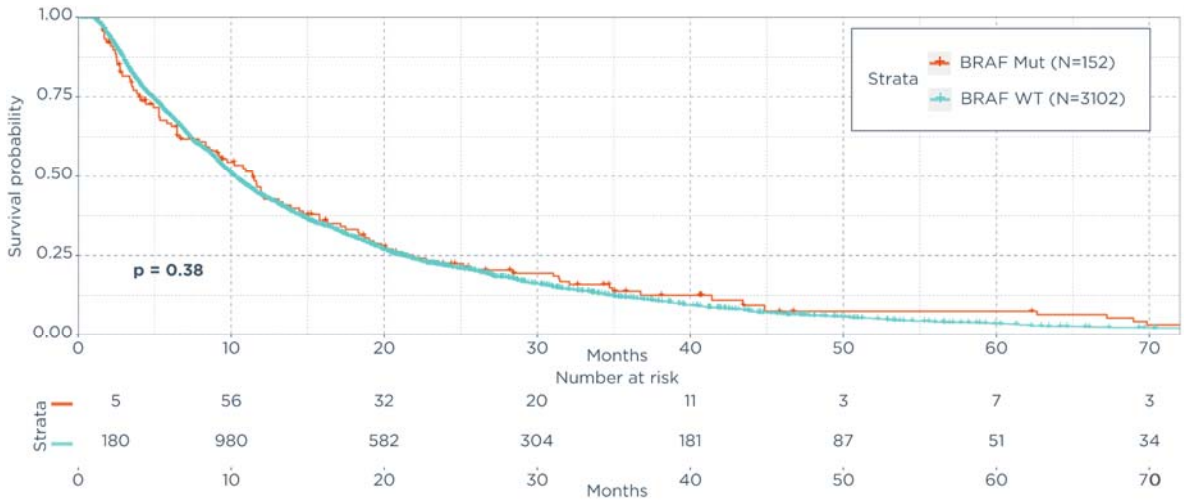
B



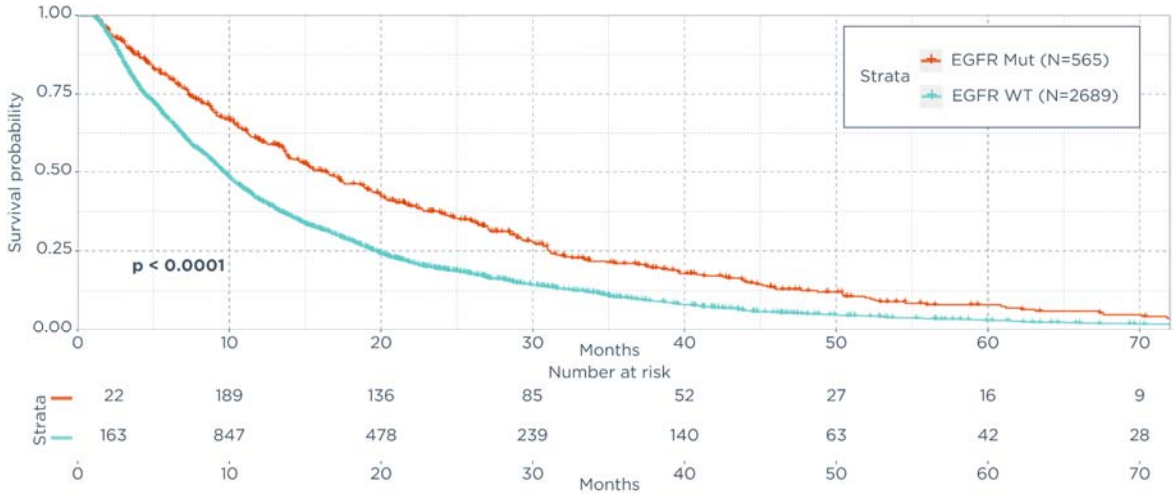
C – *ALK*



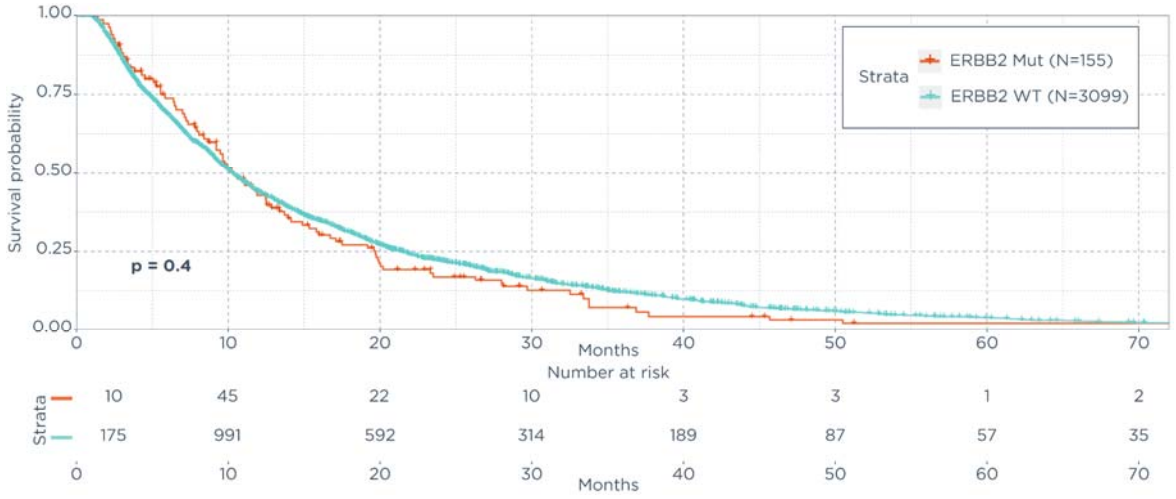
C – *BRAF*



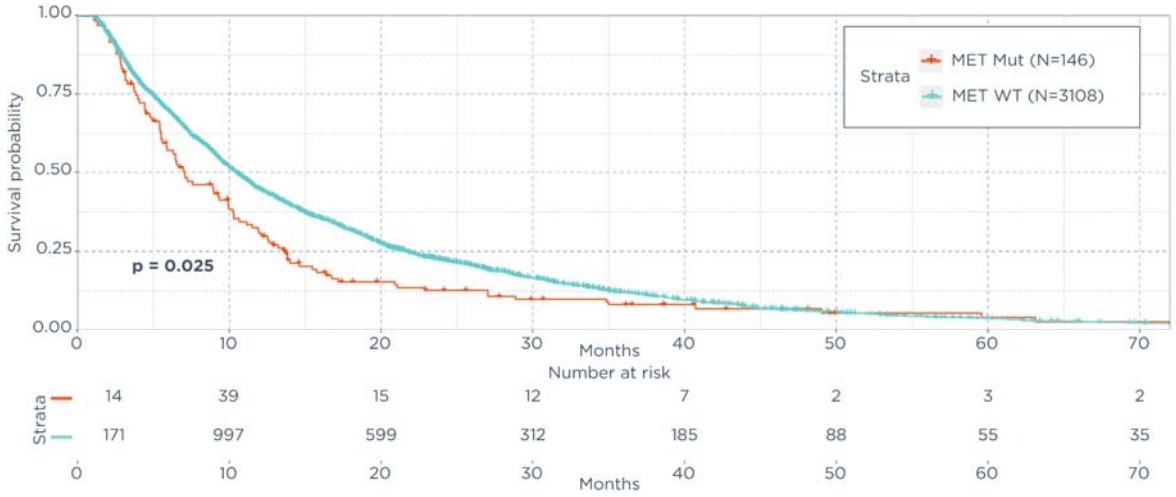
C – *EGFR*



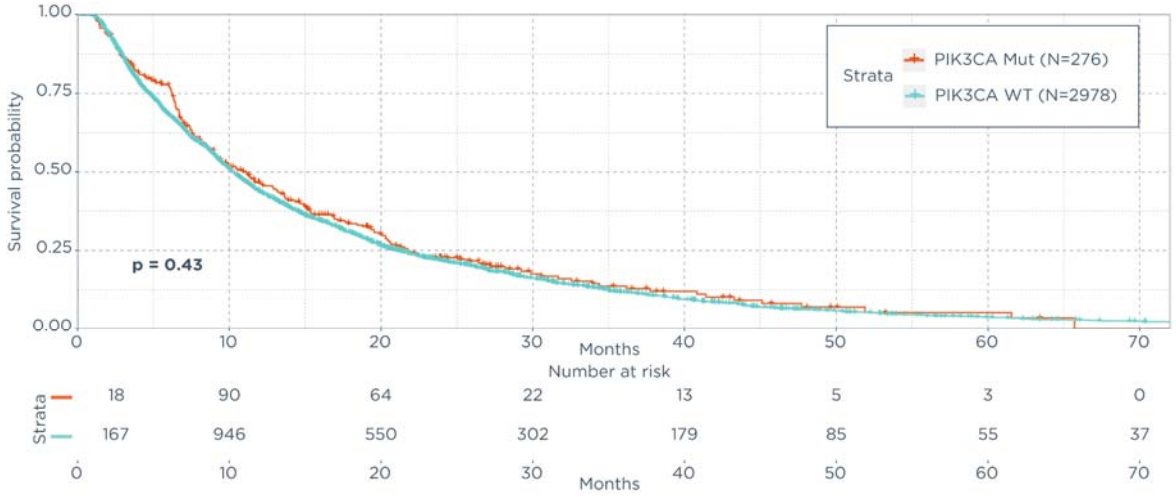
C – *ERBB2*



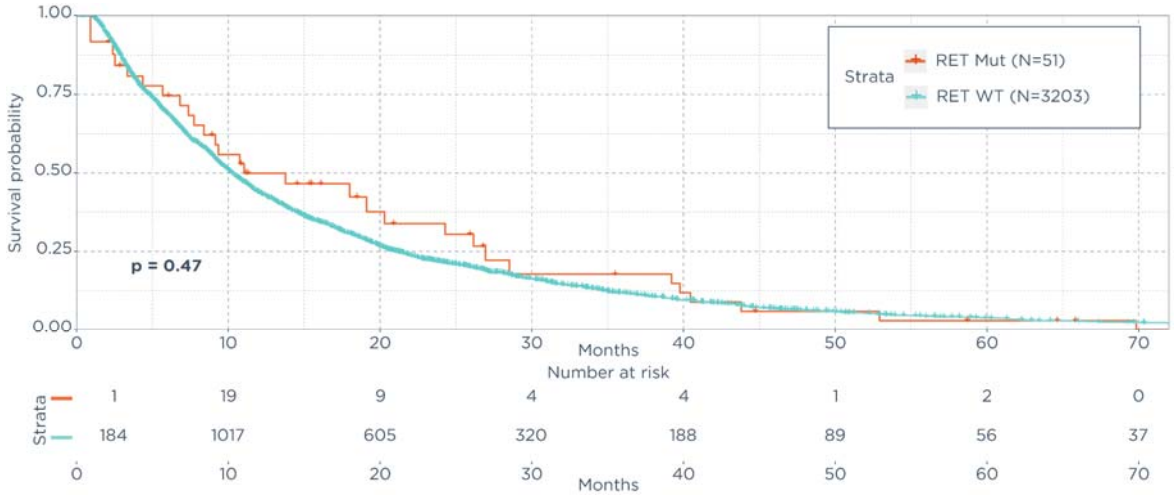
C – *MET*



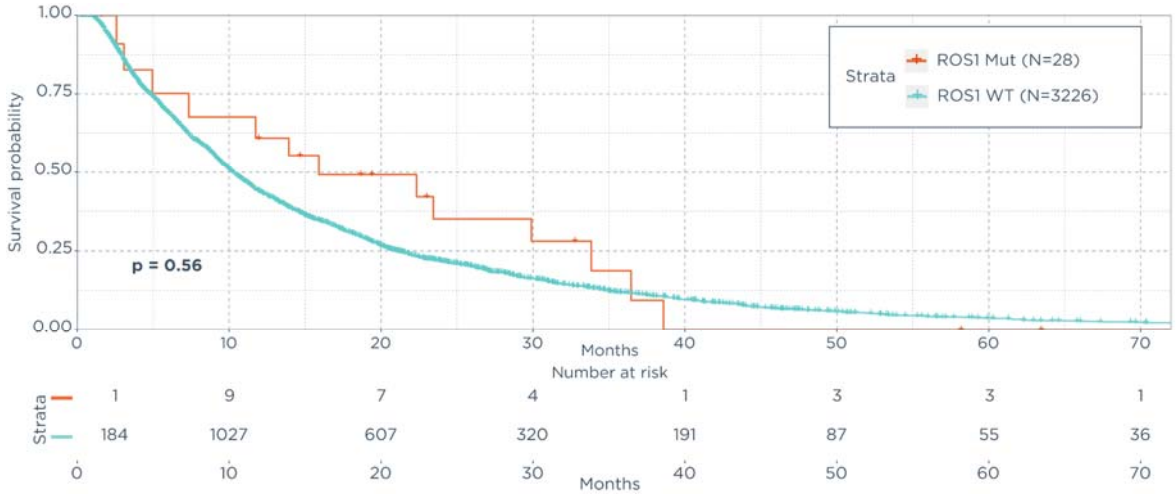
C – *PIK3CA*



C – *RET*



C – *ROS1*



eFigure 6: Genomic Predictors of Survival and Therapy Response

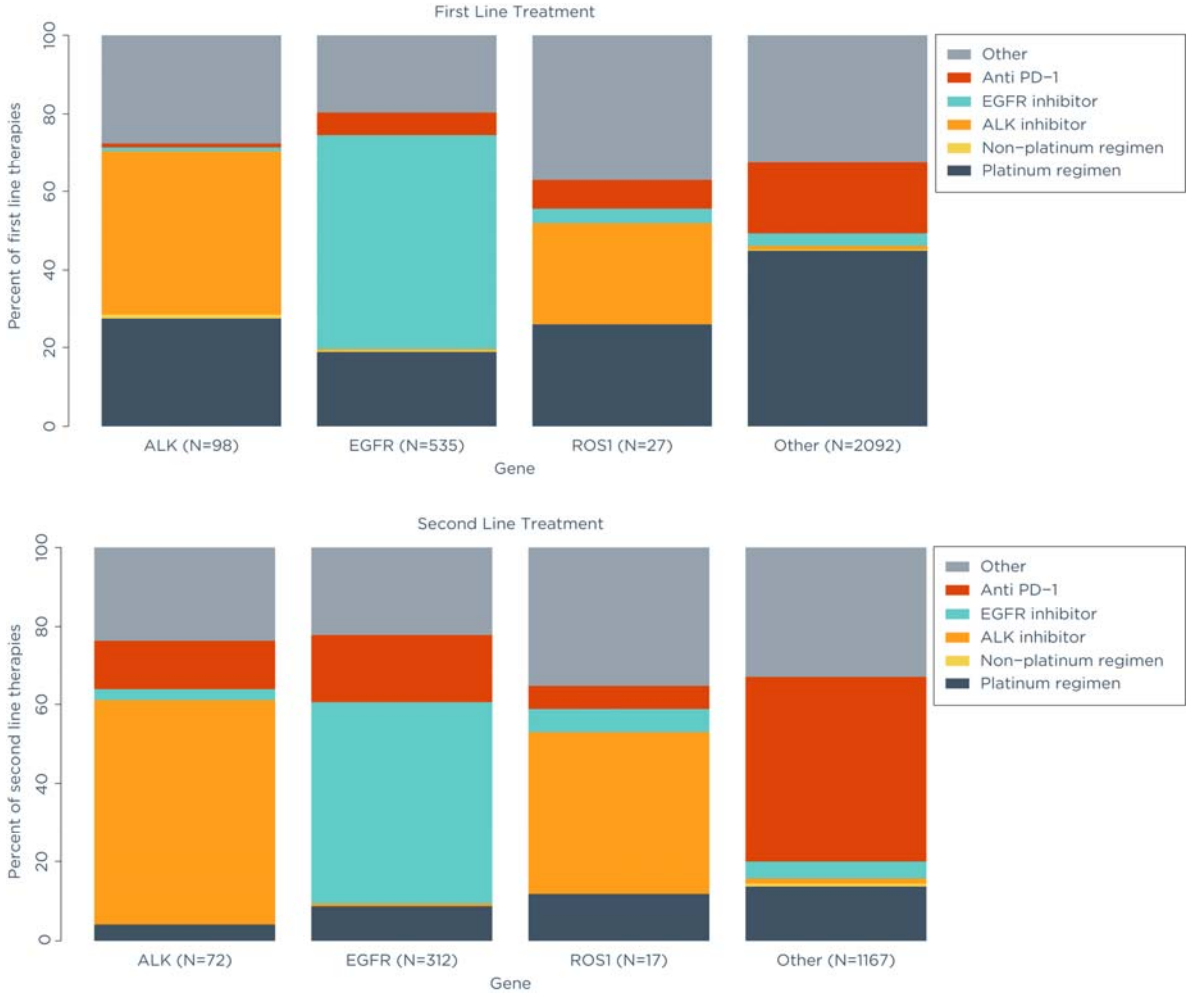
(a) Overall survival from advanced diagnosis of patients stratified by mutation status of *RB1* (top) and *TP53* (bottom)

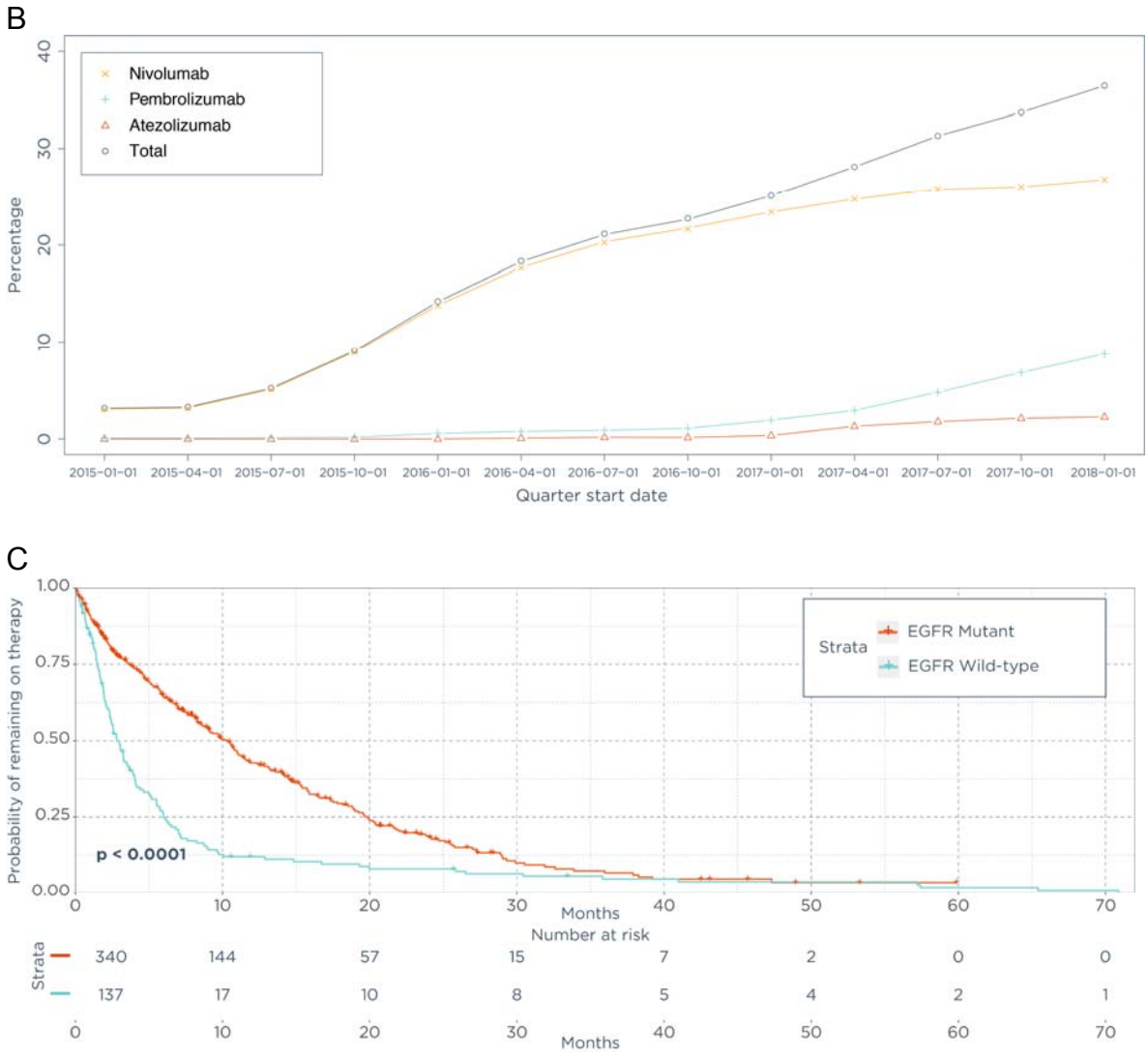
(b) Overall survival from advanced diagnosis of patients stratified by the presence of an NCCN driver mutation (NCCN drivers include *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *RET*, *ERBB2*)

(c) Overall survival from advanced diagnosis of patients stratified by presence of mutation in specified gene

eFigure 7. Genomic Predictors of Survival and Therapy Response

A





eFigure 7: Genomic Predictors of Survival and Therapy Response

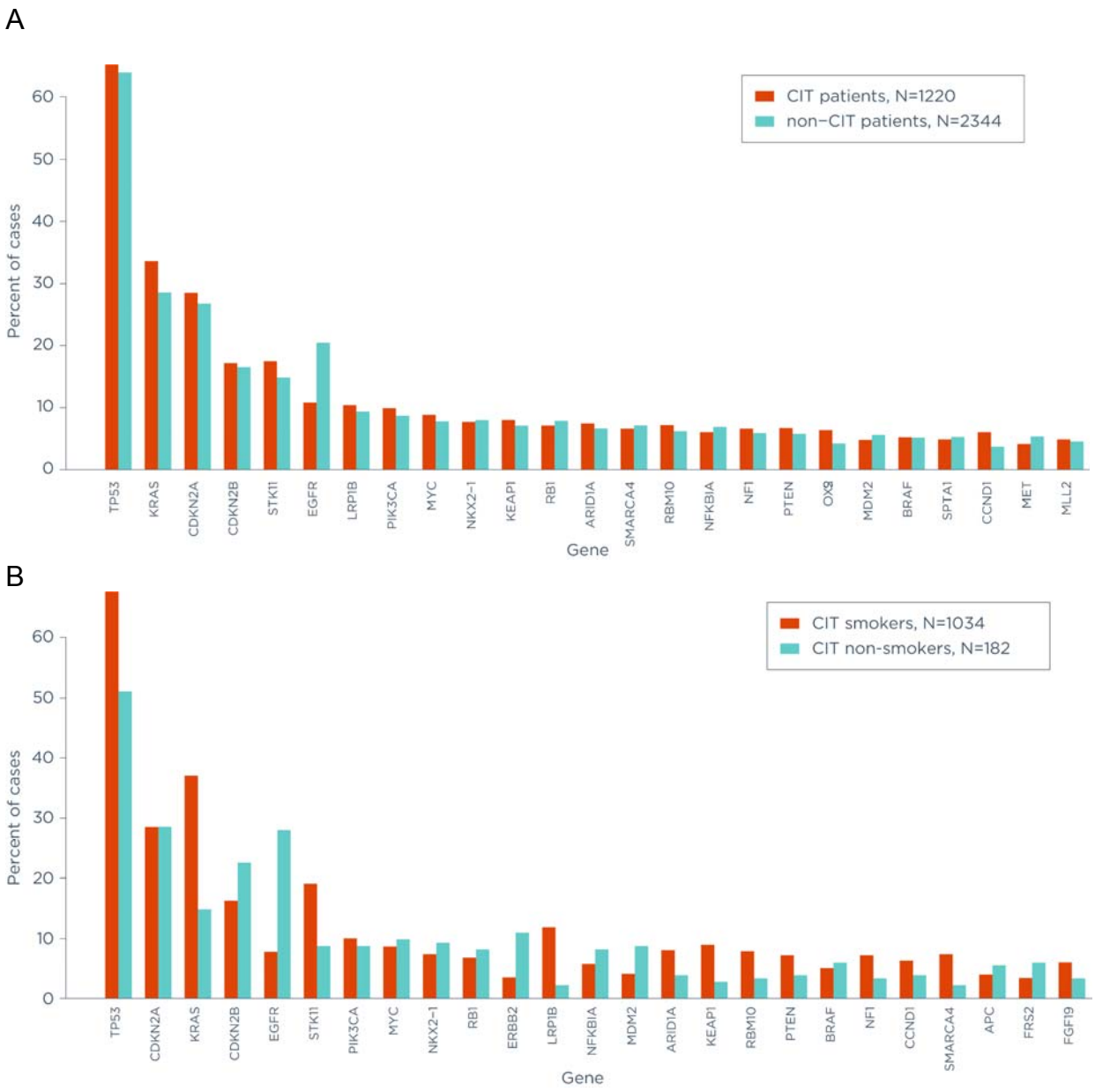
(a) First (top) and second (bottom) lines of therapy delivered to patients with advanced diagnoses, stratified by *EGFR*, *ALK*, and *ROS1* mutation status*

(b) Cumulative percentage of patients in the CGDB treated with anti-PD-1/PD-L1 therapies over time

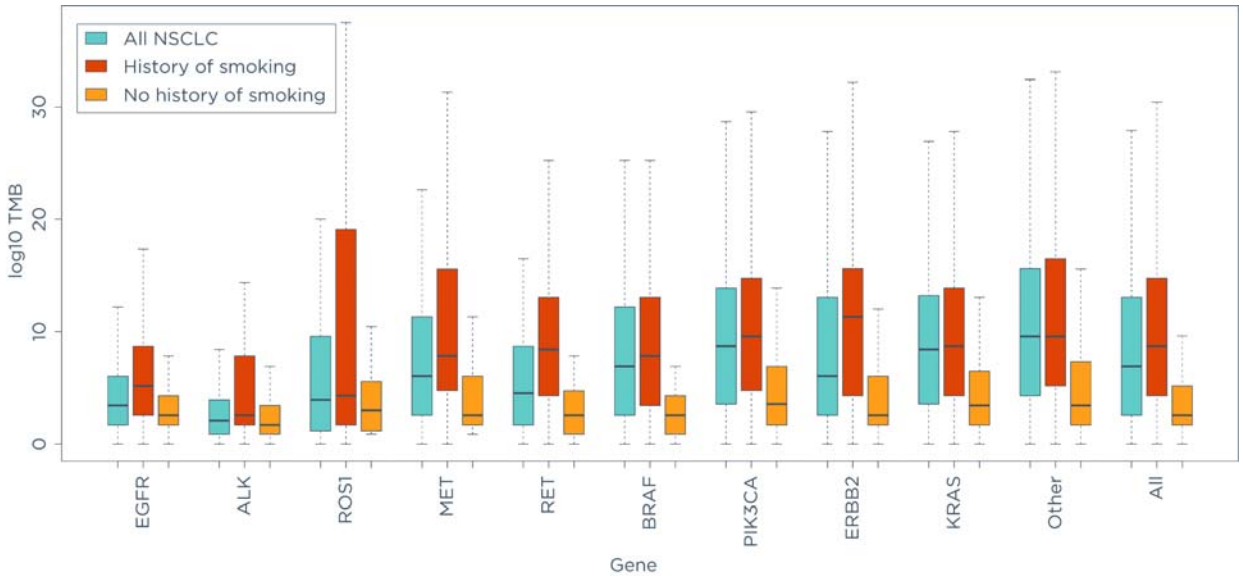
(c) Probability of remaining on therapy in patients treated with an EGFR inhibitor, stratified by presence of an *EGFR* mutation

* “Other” therapies includes anti-VEGF agents (bevacizumab or ramucirumab), anti-EGFR antibodies, single agent chemotherapies, or clinical trial therapies. These data do not include patients who did not receive systemic therapy.

eFigure 8. Tumor Mutation Burden (TMB) in Immunotherapy Treated Cohort



C



eFigure 8: Tumor Mutation Burden (TMB) in Immunotherapy Treated Cohort

(a) Distribution of top 25 mutated genes in patients that received cancer immunotherapy (CIT, anti-PD-1/PD-L1 therapy) (red) and those that did not receive CIT (green)*

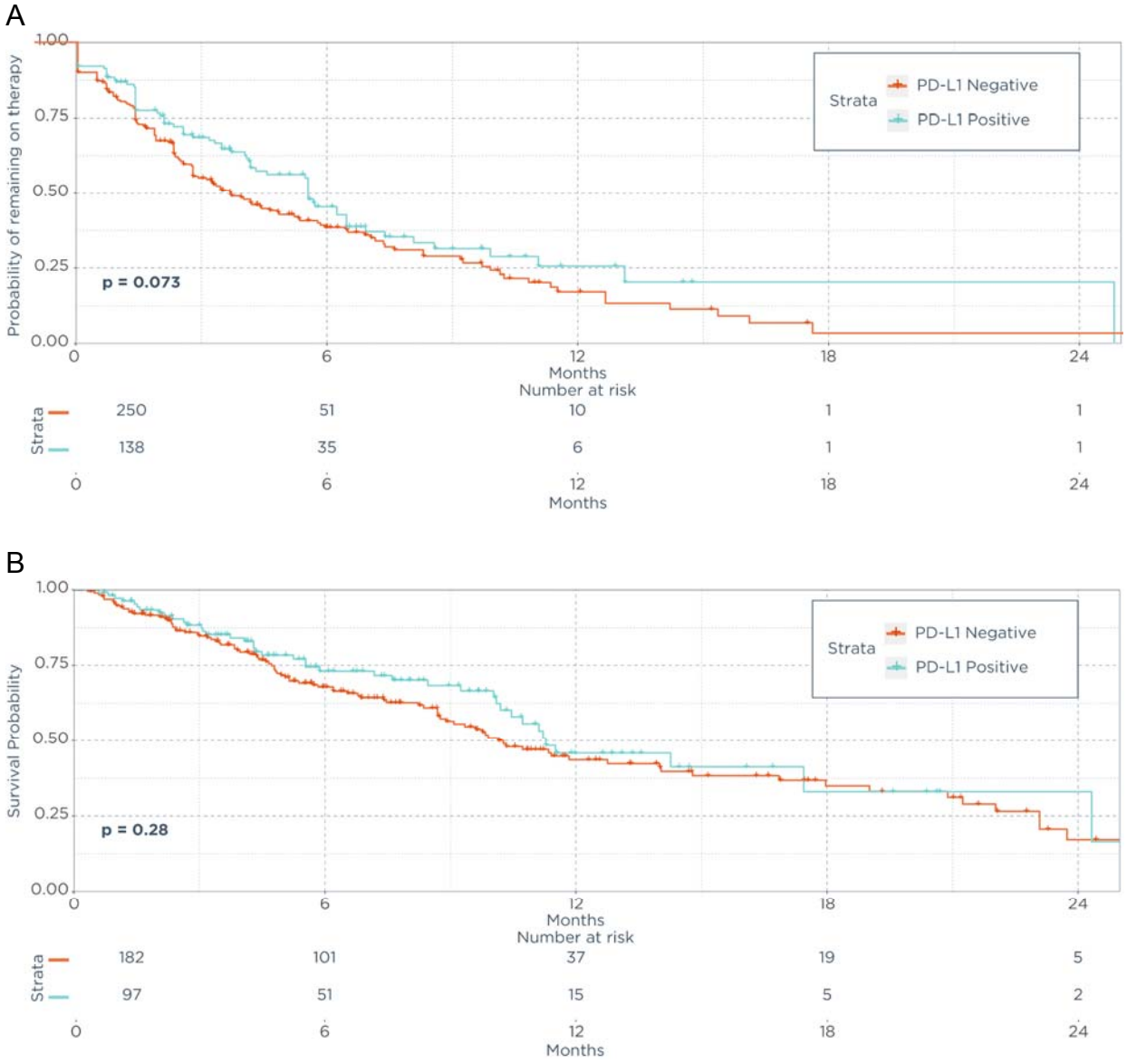
(b) Distribution of mutations in patients with a history of smoking (red) and no history of smoking (green) who received CIT*

(c) Distribution of median tumor mutational burden in anti-PD-1/PD-L1 treated patients stratified by presence of genetic mutation for all patients (green), those with a history of smoking (red), and those without a history of smoking (orange)†

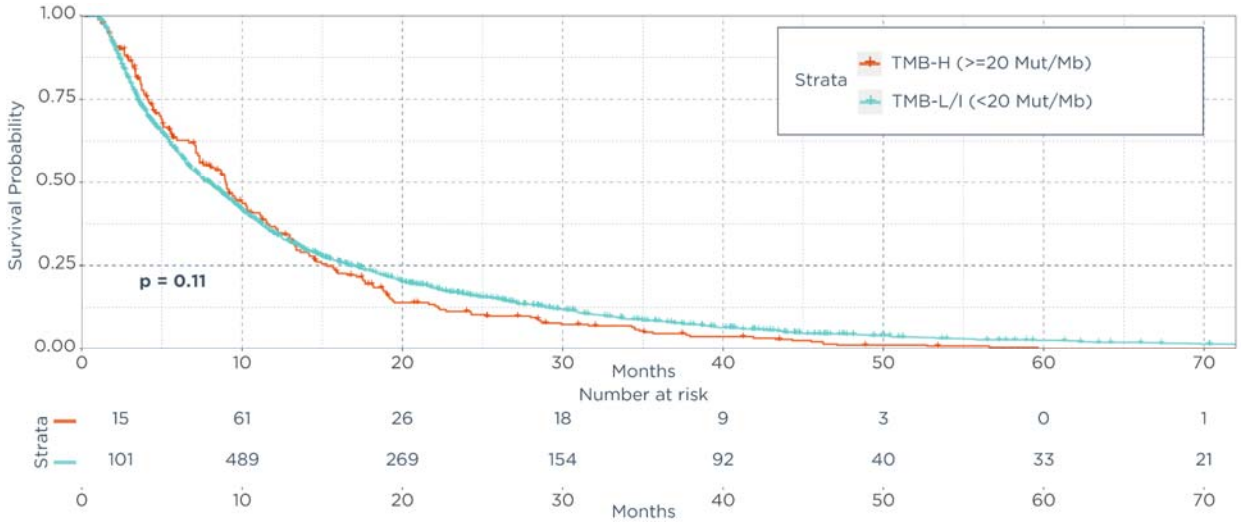
* For purposes of uniformity, only data from patients for whom tumor sequencing was done on the most updated FoundationOne platform (see eTable 1) are presented here.

† The heavy horizontal line is the median, the top and bottom edges of the box correspond to the upper and lower 25% respectively, the error bar extends to 1.5 times the interquartile range, the open circles are outliers.

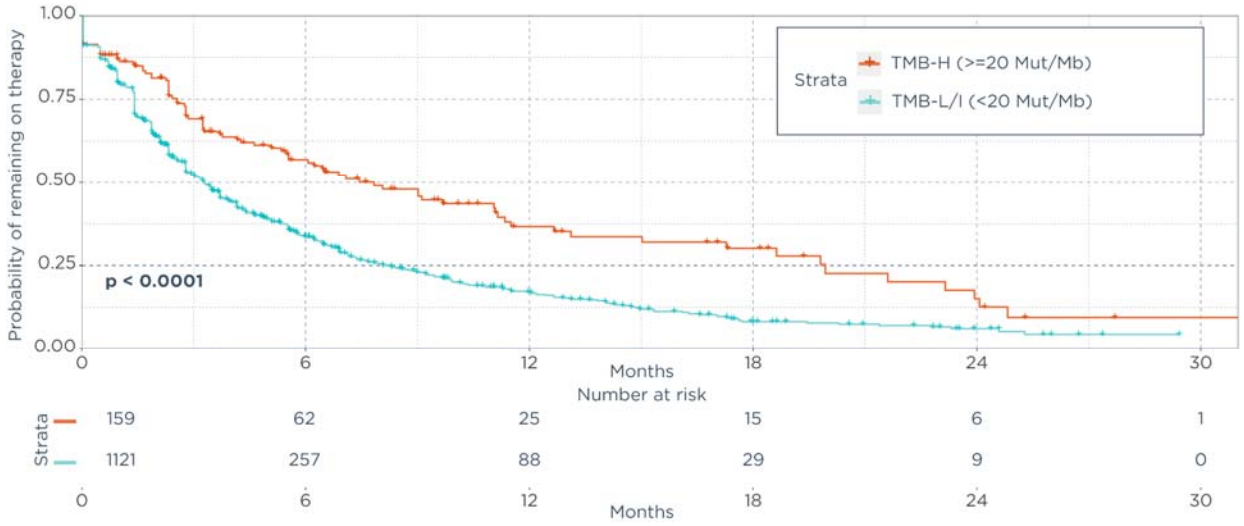
eFigure 9. Immunotherapy and Tumor Mutational Burden (TMB)



C

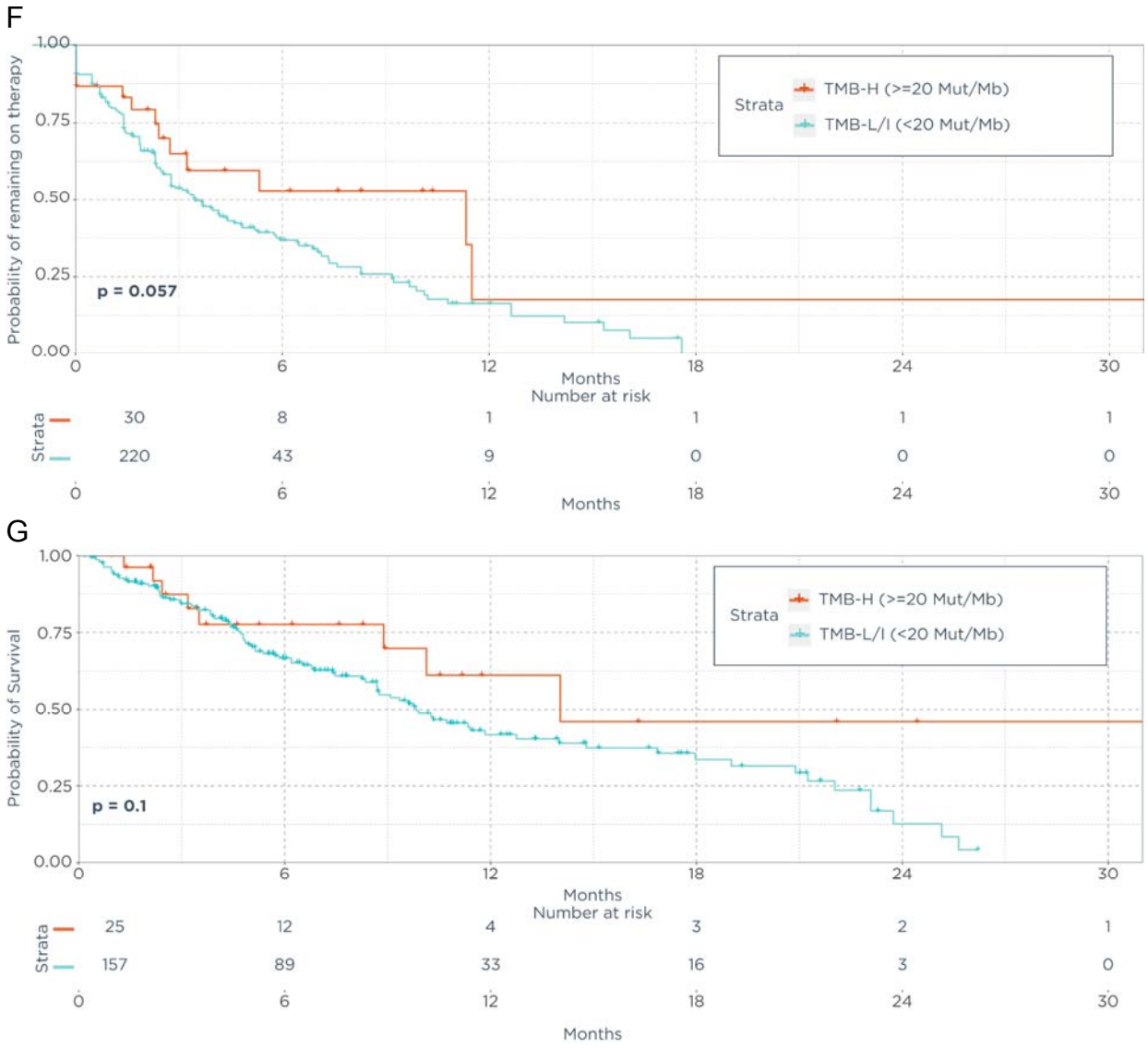


D



E

	TMB-L/I (N=789)	TMB-H (N=119)
PD	342 (43.3%)	23 (19.3%)
SD	233 (29.5%)	45 (37.8%)
PR	198 (25.1%)	46 (38.7%)
CR	16 (2.0%)	5 (4.25%)
CBR*	447 (56.7%)	96 (80.7%)
	CBR $\chi 2$ $p < 0.001$	



eFigure 9: Immunotherapy and Tumor Mutational Burden (TMB)

(a) Cumulative duration from start of anti-PD-1/PD-L1 therapy, stratified by PD-L1 status
(b) Overall survival from start of anti-PD-1/PD-L1 therapy, stratified by PD-L1 status
(c) Overall survival from advanced diagnosis of patients without anti-PD-L1/PD-1 exposure in cohort, stratified by degree of tumor mutational burden
(d) Duration on anti-PD-1/PD-L1 therapy from start of therapy, stratified by degree of tumor mutational burden (TMB-H $\geq$ 20 mutations/Mb, TMB-L/I < 20 mutations/Mb)
(e) Maximal response to anti-PD-1/PD-L1 therapy, as documented in the EHR by the treating clinician, stratified by degree of tumor mutational burden (TMB-H $\geq$ 20 mutations/Mb, TMB-L/I < 20 mutations/Mb)
(f) Duration on anti-PD-1/PD-L1 therapy from start of therapy in PD-L1 negative patients, stratified by degree of tumor mutational burden

(g) Overall survival from start of anti-PD-1/PD-L1 therapy in PD-L1 negative patients, stratified by degree of tumor mutational burden

* CBR refers to non-progressive disease, the sum of complete response (CR), partial response (PR), and stable disease (SD)

eTable 1. Composition of Patients Sequenced on the Different Versions of the FoundationOne Sequencing Platforms

FoundationOne Version	Number of Patients	Percentage of CGDB	Number of Genes Sequenced for Exonic Alterations	Number of Genes Sequenced for Rearrangements
T7	3564	87.7%	395	31
T5a	469	11.5%	287 (+34 ADME)	19
T4b	28	1.0%	222 (+34 ADME)	14

Note: ADME refers to genes related to drug bioavailability or metabolism.

eTable 2. Individual Characteristics of 4064 Non-Advanced and Advanced NSCLC With Wild Type or Altered Variants of a Gene Are Compared. For each gene, we output a traditional baseline table (based off of Table 1) of patient characteristics.

Interpretation: A p-value < 0.05 suggests that the difference in the distribution or proportion of patients with the characteristic of interest differs significantly between those patients who do or do not have that genetic alteration. For example, those NSCLC patients with an alteration in the *ALK* gene had a significantly higher proportion of squamous cell carcinoma histology when compared to those NSCLC patients who had the wild type *ALK* gene.

Note 1: When appropriate, we used the $\chi 2$ test (for categorical variables, e.g., histology) or Fisher's exact test (for categorical variables with small strata based on the expected values, <5 patients, e.g., race), and Kruskal-Wallis test (for continuous variables, e.g., age) to assess the significance of these differences between sub-cohorts.

Note 2: Only "known" or "likely" pathogenic (as annotated by Foundation Medicine) short variants, copy number variants, and rearrangements were included.

Note 3: "Advanced" disease status is defined as stage IIIB / IV disease at diagnosis or recurrent or metastatic disease at any stage.

Note 4: Summaries of characteristics related to an advanced diagnosis date (age at advanced diagnosis date, months between advanced diagnosis date and FMI test) are calculated using just those patients with an advanced diagnosis date.

Note 5: The summary of group stage excludes patients with unknown group stage.

eTable 2 (Continued)
Cohort Sociodemographic and Tumor Characteristics by EGFR

	EGFR mutant N=701	*EGFR* wild-type N=3363	p.overall
Age at advanced diagnosis (median, [IQR])	65.0 [57.0;74.0]	67.0 [59.0;73.0]	0.089
Gender:			<0.001
Female	440 (62.8%)	1669 (49.6%)	
Male	261 (37.2%)	1694 (50.4%)	
Smoking status:			<0.001
History of smoking	364 (51.9%)	2819 (83.8%)	
No history of smoking	329 (46.9%)	499 (14.8%)	
Unknown/Not documented	8 (1.14%)	45 (1.3%)	
Race:			<0.001
Asian	59 (8.4%)	67 (2.00%)	
Black or African American	28 (4.0%)	199 (5.9%)	
Hispanic or Latino	3 (0.4%)	3 (0.1%)	
Other Race	75 (10.7%)	297 (8.8%)	
Unknown/unavailable	109 (15.5%)	408 (12.1%)	
White	427 (60.9%)	2389 (71.0%)	
Disease status: Advanced	630 (89.9%)	2892 (86.0%)	0.007
Vital status: Has documented date of death	283 (40.4%)	1663 (49.4%)	<0.001
Stage of disease at initial diagnosis:			<0.001
0	0 (0.00%)	1 (0.03%)	
I	70 (10.4%)	318 (10.0%)	
II	36 (5.4%)	273 (8.6%)	
III	109 (16.2%)	737 (23.2%)	
IV	458 (68.1%)	1846 (58.1%)	
Histologic subtype:			<0.001
Non-squamous cell carcinoma	642 (91.6%)	2511 (74.7%)	
NSCLC histology NOS	18 (2.6%)	167 (5.0%)	
Squamous cell carcinoma	41 (5.6%)	685 (20.4%)	
No. of lines of therapy received:			<0.001
1	223 (31.8%)	960 (28.5%)	
2	146 (20.8%)	665 (19.8%)	
3+	166 (23.7%)	589 (17.5%)	
No line of therapy captured in database	166 (23.7%)	1149 (34.2%)	
Follow-up [days] from initial diagnosis (median, [IQR])	42.0 [16.0;85.0]	32.0 [11.0;68.0]	<0.001
Months between advanced diagnosis and FMI test dates (median, [IQR])	3.00 [1.00;18.0]	2.00 [1.00;10.00]	<0.001

eTable 2 (Continued)
Cohort Sociodemographic and Tumor Characteristics by ALK

	ALK mutant N=128	*ALK* wild-type N=3936	p.overall
Age at advanced diagnosis (median, [IQR])	58.0 [46.0;66.0]	67.0 [59.0;74.0]	<0.001
Gender:			0.709
Female	69 (53.9%)	2040 (51.8%)	
Male	59 (46.1%)	1896 (48.2%)	
Smoking status:			<0.001
History of smoking	54 (42.2%)	3129 (79.5%)	
No history of smoking	73 (57.0%)	755 (19.2%)	
Unknown/Not documented	1 (0.78%)	52 (1.32%)	
Race:			0.008
Asian	10 (7.8%)	116 (3.0%)	
Black or African American	11 (8.6%)	216 (5.5%)	
Hispanic or Latino	1 (0.8%)	5 (0.13%)	
Other Race	13 (10.2%)	359 (9.1%)	
Unknown/unavailable	12 (9.4%)	505 (12.8%)	
White	81 (63.3%)	2735 (69.5%)	
Disease status: Advanced	115 (89.8%)	3407 (86.6%)	0.345
Vital status: Has documented date of death	40 (31.2%)	1906 (48.4%)	<0.001
Stage of disease at initial diagnosis:			<0.001
0	0 (0.00%)	1 (0.03%)	
I	1 (0.8%)	387 (10.4%)	
II	8 (6.5%)	301 (8.1%)	
III	26 (21.0%)	820 (22.0%)	
IV	89 (71.8%)	2215 (59.5%)	
Histologic subtype:			<0.001
Non-squamous cell carcinoma	119 (93.0%)	3034 (77.1%)	
NSCLC histology NOS	4 (3.1%)	181 (4.6%)	
Squamous cell carcinoma	5 (3.9%)	721 (18.3%)	
No. of lines of therapy received:			<0.001
1	26 (20.3%)	1157 (29.4%)	
2	27 (21.1%)	784 (19.9%)	
3+	45 (35.2%)	710 (18.0%)	
No line of therapy captured in database	30 (23.4%)	1285 (32.6%)	
Follow-up [days] from initial diagnosis (median, [IQR])	58.5 [13.2;96.2]	33.0 [12.0;70.0]	0.003
Months between advanced diagnosis and FMI test dates (median, [IQR])	6.00 [1.00;21.0]	2.00 [1.00;11.0]	0.001

eTable 2 (Continued)
Cohort Sociodemographic and Tumor Characteristics by ROS1

	ROS1 mutant N=42	*ROS1* wild-type N=4022	p.overall
Age at advanced diagnosis (median, [IQR])	61.0 [53.0;68.8]	66.0 [58.0;73.0]	0.016
Gender:			0.017
Female	30 (71.4%)	2079 (51.7%)	
Male	12 (28.6%)	1943 (48.3%)	
Smoking status:			<0.001
History of smoking	21 (50.0%)	3162 (78.6%)	
No history of smoking	20 (47.6%)	808 (20.1%)	
Unknown/Not documented	1 (2.4%)	52 (1.3%)	
Race:			0.622
Asian	1 (2.4%)	125 (3.1%)	
Black or African American	4 (9.5%)	223 (5.5%)	
Hispanic or Latino	0 (0.00%)	6 (0.2%)	
Other Race	5 (11.9%)	367 (9.1%)	
Unknown/unavailable	6 (14.3%)	511 (12.7%)	
White	26 (61.9%)	2790 (69.4%)	
Disease status: Advanced	34 (81.0%)	3488 (86.7%)	0.386
Vital status: Has documented date of death	18 (42.9%)	1928 (47.9%)	0.617
Stage of disease at initial diagnosis:			0.955
0	0 (0.00%)	1 (0.03%)	
I	4 (10.5%)	384 (10.1%)	
II	3 (7.9%)	306 (8.0%)	
III	7 (18.4%)	839 (22.0%)	
IV	24 (63.2%)	2280 (59.8%)	
Histologic subtype:			0.142
Non-squamous cell carcinoma	37 (88.1%)	3116 (77.5%)	
NSCLC histology NOS	2 (4.8%)	183 (4.6%)	
Squamous cell carcinoma	3 (7.1%)	723 (18.0%)	
No. of lines of therapy received:			0.859
1	10 (23.8%)	1173 (29.2%)	
2	8 (19.0%)	803 (20.0%)	
3+	9 (21.4%)	746 (18.5%)	
No line of therapy captured in database	15 (35.7%)	1300 (32.3%)	
Follow-up [days] from initial diagnosis (median, [IQR])	51.0 [10.5;121]	34.0 [12.0;71.0]	0.118
Months between advanced diagnosis and FMI test dates (median, [IQR])	6.00 [1.00;39.0]	2.00 [1.00;11.0]	0.059

eTable 2 (Continued)
Cohort Sociodemographic and Tumor Characteristics by KRAS

	KRAS mutant N=1205	*KRAS* wild-type N=2859	p.overall
Age at advanced diagnosis (median, [IQR])	66.0 [58.0;73.0]	66.0 [58.0;74.0]	0.588
Gender:			<0.001
Female	733 (60.8%)	1376 (48.1%)	
Male	472 (39.2%)	1483 (51.9%)	
Smoking status:			<0.001
History of smoking	1093 (90.7%)	2090 (73.1%)	
No history of smoking	104 (8.6%)	724 (25.3%)	
Unknown/Not documented	8 (0.66%)	45 (1.57%)	
Race:			<0.001
Asian	13 (1.1%)	113 (4.0%)	
Black or African American	65 (5.4%)	162 (5.7%)	
Hispanic or Latino	2 (0.2%)	4 (0.1%)	
Other Race	95 (7.9%)	277 (9.7%)	
Unknown/unavailable	142 (11.8%)	375 (13.1%)	
White	888 (73.7%)	1928 (67.4%)	
Disease status: Advanced	1066 (88.5%)	2456 (85.9%)	0.032
Vital status: Has documented date of death	598 (49.6%)	1348 (47.1%)	0.159
Stage of disease at initial diagnosis:			0.071
0	0 (0.0%)	1 (0.04%)	
I	130 (11.4%)	258 (9.5%)	
II	102 (8.9%)	207 (7.7%)	
III	227 (19.8%)	619 (22.9%)	
IV	686 (59.9%)	1618 (59.9%)	
Histologic subtype:			<0.001
Non-squamous cell carcinoma	1070 (88.8%)	2083 (72.9%)	
NSCLC histology NOS	56 (4.7%)	129 (4.5%)	
Squamous cell carcinoma	79 (6.6%)	647 (22.6%)	
No. of lines of therapy received:			0.077
1	360 (29.9%)	823 (28.8%)	
2	242 (20.1%)	569 (19.9%)	
3+	195 (16.2%)	560 (19.6%)	
No line of therapy captured in database	408 (33.9%)	907 (31.7%)	
Follow-up [days] from initial diagnosis (median, [IQR])	32.0 [12.0;68.0]	34.0 [12.0;72.0]	0.219
Months between advanced diagnosis and FMI test dates (median, [IQR])	2.00 [1.00;10.00]	2.00 [1.00;12.0]	0.001

eTable 2 (Continued)
Cohort Sociodemographic and Tumor Characteristics by BRAF

	BRAF mutant N=202	*BRAF* wild-type N=3862	p.overall
Age at advanced diagnosis (median, [IQR])	66.5 [59.8;72.2]	66.0 [58.0;73.0]	0.793
Gender:			0.123
Female	116 (57.4%)	1993 (51.6%)	
Male	86 (42.6%)	1869 (48.4%)	
Smoking status:			0.243
History of smoking	160 (79.2%)	3023 (78.3%)	
No history of smoking	37 (18.3%)	791 (20.5%)	
Unknown/Not documented	5 (2.5%)	48 (1.2%)	
Race:			0.886
Asian	4 (2.0%)	122 (3.2%)	
Black or African American	9 (4.5%)	218 (5.6%)	
Hispanic or Latino	0 (0.0%)	6 (0.2%)	
Other Race	18 (8.9%)	354 (9.2%)	
Unknown/unavailable	24 (11.9%)	493 (12.8%)	
White	147 (72.8%)	2669 (69.1%)	
Disease status: Advanced	164 (81.2%)	3358 (86.9%)	0.025
Vital status: Has documented date of death	96 (47.5%)	1850 (47.9%)	0.974
Stage of disease at initial diagnosis:			0.816
0	0 (0.00%)	1 (0.03%)	
I	21 (10.9%)	367 (10.0%)	
II	12 (6.3%)	297 (8.1%)	
III	44 (22.9%)	802 (21.9%)	
IV	115 (59.9%)	2189 (59.9%)	
Histologic subtype:			<0.001
Non-squamous cell carcinoma	179 (88.6%)	2974 (77.0%)	
NSCLC histology NOS	8 (4.0%)	177 (4.6%)	
Squamous cell carcinoma	15 (7.4%)	711 (18.4%)	
No. of lines of therapy received:			0.041
1	41 (20.3%)	1142 (29.6%)	
2	45 (22.3%)	766 (19.8%)	
3+	40 (19.8%)	715 (18.5%)	
No line of therapy captured in database	76 (37.6%)	1239 (32.1%)	
Follow-up [days] from initial diagnosis (median, [IQR])	32.5 [11.0;73.8]	34.0 [12.0;71.0]	0.944
Months between advanced diagnosis and FMI test dates (median, [IQR])	2.00 [1.00;8.00]	2.00 [1.00;11.0]	0.664

eTable 2 (Continued)
Cohort Sociodemographic and Tumor Characteristics by MET

	MET mutant N=191	*MET* wild-type N=3873	p.overall
Age at advanced diagnosis (median, [IQR])	71.0 [63.0;77.2]	66.0 [58.0;73.0]	<0.001
Gender:			0.616
Female	103 (53.9%)	2006 (51.8%)	
Male	88 (46.1%)	1867 (48.2%)	
Smoking status:			0.029
History of smoking	135 (70.7%)	3048 (78.7%)	
No history of smoking	53 (27.7%)	775 (20.0%)	
Unknown/Not documented	3 (1.6%)	50 (1.3%)	
Race:			0.640
Asian	8 (4.2%)	118 (3.1%)	
Black or African American	6 (3.1%)	221 (5.7%)	
Hispanic or Latino	0 (0.0%)	6 (0.2%)	
Other Race	17 (8.9%)	355 (9.2%)	
Unknown/unavailable	25 (13.1%)	492 (12.7%)	
White	135 (70.7%)	2681 (69.2%)	
Disease status: Advanced	164 (85.9%)	3358 (86.7%)	0.823
Vital status: Has documented date of death	94 (49.2%)	1852 (47.8%)	0.762
Stage of disease at initial diagnosis:			0.080
0	0 (0.00%)	1 (0.03%)	
I	27 (15.1%)	361 (9.8%)	
II	8 (4.5%)	301 (8.2%)	
III	36 (20.1%)	810 (22.1%)	
IV	108 (60.3%)	2196 (59.9%)	
Histologic subtype:			0.009
Non-squamous cell carcinoma	165 (86.4%)	2988 (77.1%)	
NSCLC histology NOS	7 (3.7%)	178 (4.6%)	
Squamous cell carcinoma	19 (10.0%)	707 (18.3%)	
No. of lines of therapy received:			0.216
1	55 (28.8%)	1128 (29.1%)	
2	46 (24.1%)	765 (19.8%)	
3+	26 (13.6%)	729 (18.8%)	
No line of therapy captured in database	64 (33.5%)	1251 (32.3%)	
Follow-up [days] from initial diagnosis (median, [IQR])	24.0 [7.00;58.5]	34.0 [12.0;71.0]	0.002
Months between advanced diagnosis and FMI test dates (median, [IQR])	2.00 [1.00;9.00]	2.00 [1.00;11.0]	0.103

eTable 2 (Continued)
Cohort Sociodemographic and Tumor Characteristics by RET

	RET mutant N=70	*RET* wild-type N=3994	p.overall
Age at advanced diagnosis (median, [IQR])	64.0 [58.0;70.0]	66.0 [58.0;73.0]	0.168
Gender:			0.212
Female	42 (60.0%)	2067 (51.8%)	
Male	28 (40.0%)	1927 (48.2%)	
Smoking status:			<0.001
History of smoking	37 (52.9%)	3146 (78.8%)	
No history of smoking	32 (45.7%)	796 (19.9%)	
Unknown/Not documented	1 (1.4%)	52 (1.30%)	
Race:			0.493
Asian	3 (4.3%)	123 (3.1%)	
Black or African American	6 (8.6%)	221 (5.5%)	
Hispanic or Latino	0 (0.00%)	6 (0.2%)	
Other Race	4 (5.7%)	368 (9.2%)	
Unknown/unavailable	6 (8.6%)	511 (12.8%)	
White	51 (72.9%)	2765 (69.2%)	
Disease status: Advanced	61 (87.1%)	3461 (86.7%)	1.000
Vital status: Has documented date of death	29 (41.4%)	1917 (48.0%)	0.332
Stage of disease at initial diagnosis:			0.367
0	0 (0.00%)	1 (0.03%)	
I	5 (7.6%)	383 (10.1%)	
II	3 (4.6%)	306 (8.1%)	
III	20 (30.3%)	826 (21.8%)	
IV	38 (57.6%)	2266 (59.9%)	
Histologic subtype:			0.254
Non-squamous cell carcinoma	53 (75.7%)	3100 (77.6%)	
NSCLC histology NOS	6 (8.57%)	179 (4.5%)	
Squamous cell carcinoma	11 (15.7%)	715 (17.9%)	
No. of lines of therapy received:			0.676
1	22 (31.4%)	1161 (29.1%)	
2	10 (14.3%)	801 (20.1%)	
3+	13 (18.6%)	742 (18.6%)	
No line of therapy captured in database	25 (35.7%)	1290 (32.3%)	
Follow-up [days] from initial diagnosis (median, [IQR])	41.5 [8.75;95.8]	34.0 [12.0;71.0]	0.377
Months between advanced diagnosis and FMI test dates (median, [IQR])	3.00 [1.00;21.0]	2.00 [1.00;11.0]	0.061

eTable 2 (Continued)
Cohort Sociodemographic and Tumor Characteristics by ERBB2

	ERBB2 mutant N=186	*ERBB2* wild-type N=3878	p.overall
Age at advanced diagnosis (median, [IQR])	67.0 [59.0;73.0]	66.0 [58.0;73.0]	0.909
Gender:			0.997
Female	96 (51.6%)	2013 (51.9%)	
Male	90 (48.4%)	1865 (48.1%)	
Smoking status:			<0.001
History of smoking	107 (57.5%)	3076 (79.3%)	
No history of smoking	76 (40.9%)	752 (19.4%)	
Unknown/Not documented	3 (1.61%)	50 (1.3%)	
Race:			0.004
Asian	13 (7.0%)	113 (2.9%)	
Black or African American	10 (5.4%)	217 (5.6%)	
Hispanic or Latino	2 (1.2%)	4 (0.10%)	
Other Race	20 (10.8%)	352 (9.1%)	
Unknown/unavailable	26 (14.0%)	491 (12.7%)	
White	115 (61.8%)	2701 (69.6%)	
Disease status: Advanced	167 (89.8%)	3355 (86.5%)	0.241
Vital status: Has documented date of death	92 (49.5%)	1854 (47.8%)	0.714
Stage of disease at initial diagnosis:			0.678
0	0 (0.00%)	1 (0.03%)	
I	13 (7.4%)	375 (10.2%)	
II	13 (7.4%)	296 (8.1%)	
III	39 (22.2%)	807 (22.0%)	
IV	111 (63.1%)	2193 (59.7%)	
Histologic subtype:			0.052
Non-squamous cell carcinoma	157 (84.4%)	2996 (77.3%)	
NSCLC histology NOS	8 (4.3%)	177 (4.6%)	
Squamous cell carcinoma	21 (11.3%)	705 (18.2%)	
No. of lines of therapy received:			0.145
1	62 (33.3%)	1121 (28.9%)	
2	31 (16.7%)	780 (20.1%)	
3+	42 (22.6%)	713 (18.4%)	
No line of therapy captured in database	51 (27.4%)	1264 (32.6%)	
Follow-up [days] from initial diagnosis (median, [IQR])	32.0 [14.0;60.5]	34.0 [12.0;71.0]	0.579
Months between advanced diagnosis and FMI test dates (median, [IQR])	2.00 [1.00;11.0]	2.00 [1.00;11.0]	0.521

eTable 3. Real-World Maximal Response to Therapy (rwMTR) for Patients Treated With an EGFR Inhibitor Stratified by the Presence of a Mutation

Interpretation: A p-value of < 0.05 suggests an association between mutation status and response to the corresponding targeted agent, as defined by the sum of stable disease, partial response, and complete response.

	EGFR Inhibitor Therapy		
	EGFR Mutant (n=330)	*EGFR* WT (n=116)	
Progressive Disease	46	59	
Stable Disease	68	39	
Partial Response	195	16	
Complete Response	21	2	
Progressive Disease	46	57	
Clinical Benefit Rate (SD+PR+CR)	284	59	
p-value for association	p < 0.01		

eTable 4. Cox Multivariable Analysis for Risk of Discontinuing CIT

Variable	HR	Lower 0.95	Upper 0.95	P-value
Line CIT administered*	1.19	1.04	1.36	0.010
TMB (per 10 mut/Mb)	0.78	0.65	0.95	0.011
Male	1.32	0.98	1.78	0.072
PD-L1 Positive	0.82	0.60	1.12	0.206
Never smoker	1.27	0.84	1.92	0.256
NOS histology†	1.23	0.86	1.76	0.258
Age at Advanced Diagnosis**	1.01	0.99	1.02	0.427
Black Race‡	1.13	0.38	3.36	0.825
Squamous histology†	1.04	0.68	1.60	0.845
EGFR WT	0.95	0.55	1.64	0.859
KRAS WT	1.02	0.72	1.45	0.909
ALK WT	1.13	0.12	10.96	0.917
Non-Asian/Black/White Race‡	1.04	0.37	2.97	0.935
White Race‡	1.02	0.40	2.60	0.973

Notes:
* Line CIT Administered refers to each additional line after the first line of therapy that CIT was first administered. For example, initial CIT administration in the third line would confer a HR of 1.42 (1.19 x 1.19) of discontinuing therapy compared to first line.
** For every additional year of age
† Histology HR is relative to adenocarcinoma histology
‡ Race HR is relative to Asian race